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THE POTASSIUM AND WATER CONTENTS OF CAT NERVES AS AFFECTED BY STIMULATION

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(Received November 1, 1937.)

A LOSS of potassium from unmyelinated crab nerve has been reported by Cowan ('34) and has been recently confirmed with somewhat improved technique by Young ('38). Vogt ('36) has reported losses of K from the cervical sympathetic ganglion during stimulation. No observations have apparently been made on myelinated nerves except two experiments (Fenn, '34) on frog nerves which showed only losses of K and of Cl too small to be significant. In this paper experiments are reported on the sciatic nerve of the cat. In part, the observations were incidental to other experiments on the loss of potassium from cat muscle (Fenn and Cobb, '36) when stimulated through its nerve.

METHODS

While details differed in the various experiments, the usual procedure consisted in cutting the sciatic nerve on both sides of the cat as far centrally as possible and stimulating on one side through shielded silver electrodes with either a continuous or intermittent tetanus for 30 minutes or more. The branch of the nerve supplying the hamstring muscles was cut. After stimulation, the animal was bled to death and both sciatic nerves were dissected out, omitting 2 cm. at the central end which had been between or just below the electrodes. The tibial branch was dissected out to the gastrocnemius muscle and the superficial peroneal to the ankle. Both nerves were treated as much alike as possible during the dissection, with care to avoid undue drying and inclusion of any of the surrounding tissues. The nerves were weighed fresh in weighing bottles, dried at 100°C. to constant weight, ashed in a muffle furnace at 500°C. and analyzed for potassium by a slightly modified Shohl and Bennett method. Each nerve weighed about 0.5 gram and contained about 0.8 mgm. of potassium, an amount well within the range of the method. The accuracy of the analyses for which I am mostly indebted to my assistant, Mrs. Doris Cobb Marsh, has been checked in many previous investigations. The average difference between the potassium contents of paired nerves has been found to be 2 per cent (Fenn and Cobb, '35). A single control experiment in which both nerves were unstimulated showed changes as large as those usually observed in stimulation experiments and indicated that nothing could be gained by a more extensive control series.

RESULTS

A total of twenty-four experiments were completed and the results are summarized in Table 1. The water and potassium contents of the resting nerves were quite variable, presumably because of varying amounts of myelin

sheath, fat, and connective tissue. The potassium figures were equally variable, whether calculated per 100 grams of nerve water or per 100 grams of dry tissue, so that the variation was not all due to different amounts of nonaqueous solid material, but partly due, presumably, to varying amounts of axones.

TABLE 1

Summary of twenty-four experiments

	Normal content	Probable error of mean	Range	Change due to stimulation	Out of 24 cases
Water: cc. per 100 gms. dry	196.0	±2.1	164–240	+5.6 ±2.1	14 gains
Water: cc. per 100 gms. wet	66.2	±0.07	62– 70	+1.9 ±0.7	14 gains
Potassium: m.-eq. per 100 gms. dry	14.1	±0.2	11– 17	+0.09 ±0.19	10 gains
Potassium: m.-eq. per 100 gms. water	7.3	±0.09	6.4–8.5	−0.15 ±0.06	17 losses

The changes in water and potassium caused by stimulation were in general small, and none of the average changes shown in the table were really significant as indicated by the probable errors of the means which are included in the table. In general, about half of the nerves showed gains and half losses. The most nearly consistent result was obtained from the potassium changes calculated per 100 grams of nerve water. The figures showed that seventeen out of twenty-four nerves lost potassium but the average loss was only 2.5 times the probable error. If there is any loss of potassium, therefore, it amounts to less than 2 per cent and is too small to be detected with certainty by this method.

While a statistical study shows that the changes observed on stimulation were not significant, some of the changes were too large to be accounted for purely by the analytical error. The largest of these were losses of both potassium and water, or gains of both potassium and water (per 100 grams of dry weight) amounting to 15–25%. Such results might be due to the inclusion of more nonaqueous material with one of the nerves than with the other; they were particularly evident in the first few experiments where the dissection may have been less skillful. Moreover, the ratio $\Delta H_2O/\Delta K$ in these extreme cases was closely similar to the ratio of H_2O/K in the original nerve. Other occasional variations were probably attributable to some experimental error. Many attempts were made to obtain more consistent results by varying the nature of the stimulation, or the condition of the animal, or by better preservation of the blood supply of the nerve, but the results were always disappointing.

It is necessary to conclude, therefore, that any mobilization of K or gain of H_2O which may occur is so delayed by the medullary sheath that the net change is inappreciable. Or the change due to each impulse is so small that recovery is complete before the arrival of the next one. It is also possible that the electrolyte changes are purely secondary phenomena, dependent upon the

recovery processes so that conduction can occur in cat nerves without a loss of potassium.

Summary

Cat nerves stimulated continuously in situ for 30 minutes or more at a frequency of 50–100 per second show no consistent loss or gain of potassium or water.

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THE EFFECT OF STIMULATION ON THE POTASSIUM CONTENT OF LIMULUS LEG NERVES

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THE RESULTS of experiments on the potassium loss in nerves during stimulation have led to no definite general conclusion. Fenn ('38) working with the myelinated nerves of cats and frogs obtained no significant loss of potassium. Cowan ('34) using the unmyelinated nerves of the spider crab, *Maia squinado*, obtained an appreciable loss of potassium during fifteen minutes of stimulation. His method, however, is open to two criticisms: (1) The sections of nerves from which the potassium was lost, were between the stimulating electrodes. (2) No criterion was used to determine whether the nerves were conducting during stimulation. It seemed important therefore, to determine again the effect of stimulation on unmyelinated nerve with appropriate modifications of the technique.

METHOD

Initially, experiments were started using the nerves of the spider crab, *Libinia emarginata*, but were discontinued due to the rapid loss of excitability. The leg nerves of *Limulus polyphemus* were then chosen since they could be easily dissected out and retained their excitability, provided the enclosing vascular sheath was not removed.

The legs were cut off at their junction with the body, threads were tied around the proximal end of the nerves, and the nerves dissected from all but the two most distal segments of the legs. These preparations were kept in running sea water for at least one-half hour before using. Corresponding nerve-muscle preparations from the opposite sides of the animal were used as experimental and control preparations respectively.

The two preparations were placed in a dish of sea water and the claw of the experimental preparation was connected to an isometric lever. The experimental nerve was then stimulated at a frequency of one hundred and fifty shocks per second for fifteen minutes or more, by means of a thyratron stimulator. The tension maintained by the claw dropped to about 50 per cent of its initial value after fifteen minutes stimulation. The control nerve was tested at the beginning and end of stimulation, and only those preparations which showed contraction of the claw and abduction at the first joint were used.

After stimulation, the nerve of the experimental preparation was cut where it entered the second joint, and again just distal to the stimulating electrodes. It was then blotted on filter paper; weighed on a torsion balance, and trans-

ferred to a weighing bottle. The corresponding section of the control nerve was excised and treated similarly.

After drying to constant weight at 100°C. the nerves were analyzed for potassium using the modification of Shohl and Bennett's method described by Fenn and Cobb ('36).

Twenty-three pairs of nerves were analyzed. Of these, four experiments were discarded for obvious technical errors. Of the remaining nineteen, three had no dry weight determinations.

The results of these experiments are:

Average per cent loss of potassium $= 3.15 \pm 2.1$ (P.E. of mean) Calc. on wet wts. 19 expts.

Average per cent loss of potassium $= 4.2 \pm 1.7$ (P.E. of mean) Calc. on dry wts. 16 expts.

The above results are hardly significant, probably because of dissimilarity in control and stimulated nerves. A suitable procedure for eliminating those preparations in which control and stimulated nerves are different seems to be on the basis of comparison of dry wt./wet wt. between the control and stimulated preparations.

In the above sixteen experiments with wet and dry weights the average per cent difference of the ratio dry wt./wet wt. is 0.2 ± 1 (P.E. of mean) indicating no significant change in water content in either direction as a result of stimulation. Three of the above pairs however, had differences in the ratios (dry weight/wet weight) of -12.8 per cent, 9.3 per cent and 10.2 per cent respectively. These differences are so large compared with the probable error of the average of this ratio that they could only have been due to very dissimilar control and experimental preparations. There is justification therefore for omitting these three experiments also.

For the remaining thirteen experiments, eleven of which showed a loss as indicated in Table 1, the average per cent loss of potassium was:

(a) 6.1 ± 1.2 (P.E. of mean) calc. on wet wts.

(b) 7.0 ± 1.2 (P.E. of mean) calc. on dry wts.

The averages of Cowan's results for a 15 minute stimulus on Maia nerves as calculated from his paper are:

Loss of potassium at 40 shocks per sec. $= 5.9$ per cent based on wet wts.

Loss of potassium at 100 shocks per sec. $= 7.4$ per cent based on wet wts.

Loss of potassium at 140 shocks per sec. $= 6.9$ per cent based on wet wts.

Summary

Analyses for potassium in the leg nerves of *Limulus polphemus* showed a loss of six to seven per cent of the potassium during a tetanus of fifteen minutes. This is in agreement with the results of Cowan on the loss of potassium from the leg nerves of *Maia squinado*.

Acknowledgments are due to Mrs. Doris Cobb Marsh for the potassium analyses, to Dr. W. O. Fenn who initiated the experiments, for his advice and assistance, and to Dr. M. H. Jacobs for extension of facilities at the Marine Biological Laboratory.

TABLE 1

Weights and potassium contents of limulus nerves

Wet wt. mgms.		Dry wt. mgms.		Potassium mgm. % wet wt.	
Control	Stimulated	Control	Stimulated	Control	Stimulated
132	105	17	13.5	510	544
51	53.5	9.8	10.8	446	360
70.5	75	12.2	13.0	561	486
138	136	22.9	22.3	409	369
151	137	26.7	23.4	380	388
119	118	21.0	20.5	379	347
80	81.5	13.4	14.0	436	431
127	140	21.4	23.1	444	386
130	115	20.6	19.4	434	423
*52	54	17.9	18.1	735	683
65	72.5	10.0	11.8	546	513
95.5	88.5	15.1	13.5	506	454
72.0	67	13.0	12.5	488	486

* Sheaths dissected off before weighing and analyzing.

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THE NON-CENTRIFUGAL DEGENERATION OF SEVERED PERIPHERAL NERVE

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INTRODUCTION

NEUMANN in 1868 proposed the idea that severed peripheral nerve degenerates centrifugally; i.e., the degenerative processes start at the cut end and progress slowly towards the periphery. This view, opposing the conception of simultaneous degeneration advanced by Lent in 1856, started a controversy as yet unsettled. Most of the arguments on both sides have been based on histological evidence—only relatively recently has there been any physiological experimentation on the subject. The early physiological studies were concerned chiefly with the time of disappearance of indirect excitability of the muscles innervated by cut nerves (Bethe, 1903; Courrier, 1926).

Apostolaki and Deriaud (1925) found no change in chronaxie following section until the "complete degeneration" of the nerve (i.e., loss of indirect excitability of the muscle). This occurred by 9–10 days in frogs kept at 12–15°C. The nerve's rheobase increased by the fourth day after the cut, but there was no appreciable change in gastrocnemius chronaxie for 20–30 days. Titeca (1932, 1935) confirmed this for frogs kept at 22°C. (no change in chronaxie for 8 days). He also described an early "fatiguability," manifested as an increasing threshold with repeated stimulation. This was found to progress slowly centrifugally and was correlated by him with Parker's observations on centrifugal degeneration of motor fibers of the frog sciatic (Parker, 1933) and of myelin sheaths of the lateral line nerves of catfish (Parker and Paine, 1934). On the other hand, Titeca reported that action potentials disappeared simultaneously all along the degenerating frog nerve. Koch (1925) had earlier shown a uniform loss of resting potential throughout degenerating mammalian nerve.

More recent experiments on rats and frogs (Hołobut and Jałowy, 1936) again showed no change in chronaxie until loss of indirect excitability, and the uniform loss of action potential along a cut nerve (indirect excitability disappeared at 6–9 days at a temperature of 10–12°C.; Hołobut, 1937).

In view of the discrepancy between the action potential findings, which indicate simultaneous degeneration of frog nerve, and the evidence for centrifugal degeneration obtained from twitch heights, histology, and fatiguability, it seemed desirable to study several of these attributes on the same preparations.

METHOD

Winter and spring frogs (*Rana pipiens* and *R. sylvatica*) were kept in a large tank, with a constant flow of water sufficient to maintain a layer half a centimeter deep. Only healthy animals were used. Under light ether anesthesia, the skin on the back was cleaned

with alcohol, an incision, about 1 cm. long, made between the urostyle and the ilium, the underlying muscles separated with fine-pointed forceps, and the sciatic plexus revealed. Avoiding adjacent blood vessels, the left sciatic trunk was picked up on a pair of curved forceps and sectioned with sharp scissors just below the anastomosis of the spinal nerves. The cut ends of the nerve were allowed to slip back, the muscles drawn together, and the lining of the dorsal lymph sac and the skin were closed, usually together, with one or two silk sutures. In most cases, healing occurred rapidly: infected animals and those which developed red leg were discarded.

In the first series, frogs were kept at a temperature between 18°C. and 20°C.: in the second, between 12°C. and 15°C. For these longer experiments, the frogs were forced-fed with small bits of chopped meat. Only those animals vigorous at the time of examination were used.

From 1 to 20 days after operation, a frog was pithed and immobilized, and both sciatic nerves dissected free without injury to the blood vessels of the leg. In all experiments, the left (operated) and right (control) nerves were treated alike as far as possible. For the kymograph records the usual gastrocnemius-muscle-lever set-up was used except that the femoral end of the muscle was left intact so that its circulation remained unimpaired and the bone was clamped *in situ*. In a number of experiments records were taken simultaneously from the gastrocnemius and from the peroneal group of muscles. The same length lever arms were used with both right and left sides to permit a roughly quantitative comparison.

The nerve was stimulated using bipolar metal electrodes 1 mm. apart from a Harvard inductorium with 6 volts in the primary and with the secondary, to start with, at 13 cms. and an angle of 5° from vertical. In no case was it necessary, in order to get maximal responses, to have the coil horizontal at less than 9 cms. The electrodes were placed at three positions: H, 1–2 cms. below the cut end (to avoid the area of traumatic degeneration), M, just before the bifurcation of the sciatic to form tibialis and peroneal nerves, and, K, at the knee. Each region was tested in order with progressively stronger stimuli, from subthreshold to slightly supramaximal. To minimize as much as possible the inevitable fatigue (which is more pronounced in the operated nerve), the whole preparation was repeatedly washed with Ringer's solution. This procedure eliminated bizarre results found in preliminary experiments, such as a period of inexcitability between two periods of good excitability.

After muscle responses were recorded, the nerves were removed and their action potentials studied with the cathode-ray oscillograph (Gerard, Marshall, and Saul, 1936). The trace was sometimes photographed, more often measured on the screen. A standing wave was obtained by using a commutator interrupter in the primary of the inductorium. The central end of the nerve was placed on stimulating electrodes and a pair of silver lead electrodes, 1 cm. apart, moved along the nerve. Change of spike height with distance was compared for normal and sectioned nerves.

In a few cases, with conduction on the verge of failing, extensive kymograph records were omitted and only tests for the presence of indirect excitability carried out before removing the nerve. Other frogs from the same batch and in the same operative period were then used for the contraction height measurements. This was necessitated by the excessive fatiguability of such nerves.

In all cases, following these tests, the nerves were examined histologically.* A few were washed, teased, and immersed in 1:10,000 neutral red, according to the method of Covel and O'Leary (1932). The majority were fixed in 10 per cent formol in 0.7 per cent NaCl or in H_2O, teased, and stained with a modified Herxheimer stain by the following procedure:

1. Cover slide upon which nerve is teased with Sudan III (Romeis, 1929) for ten minutes
2. Wash rapidly (distilled water) until wash water is almost clear
3. Flood with 1% aqueous haematoxylin for five minutes
4. Wash off excess stain with distilled water
5. Flood with 1 per cent ferric chloride for 1–5 minutes, depending on intensity of stain desired
6. Wash well with tap water
7. Mount in glycerine jelly, after complete teasing of nerve.

* The Marchi stain was not used because it is held (Cajal, 1928) not to show accurately the myelin configuration in the early stages of degeneration.

The whole process is carried out on the slide: with practice the nerve does not come off. Final teasing with steel needles or quills under a strong dissecting microscope clearly exposes individual nerve fibers for comparatively long distances (1–2 cms.). The myelin products appear orange-red, the nucleus and cytoplasm deep blue, and, if washing was adequate, the preparation lasts at least two months.

Camera lucida drawings were made of significant preparations.

In all, over 75 frogs were examined 2–20 days after nerve section, and of these about a third in 12–16 days, the period supposed to show progressive degeneration most clearly. To eliminate the possibility of missing any progressive degeneration because of too rapid degeneration at 18°–20°C., a second series of frogs was run at 12°–15°C. Except for a prolonged time scale in the latter case, the results in the two series were the same. In addition, a series of 8 rats was run to confirm the simultaneous degeneration of mammalian (monkey and cat) sciatic nerves described by Heinbecker, Bishop, and O'Leary (1932).

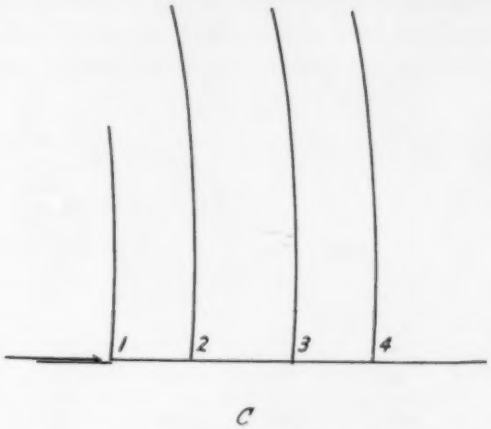

FIG. 1. Kymograph records of gastrocnemius twitches caused by stimulation of a normal sciatic nerve with submaximal shocks (secondary at 13 cms., 5° from vertical), showing the shunting effects of branches.

1. Tibialis nerve central to muscular branch.
2. Tibialis nerve peripheral to muscular branch.
3. Same as 1, after stripping back muscular branch.
4. Same as 2.

RESULTS

When adequate stimuli are applied to various points along the sciatic nerve, the gastrocnemius contracts to the same degree for all electrode positions. The contrary findings of Parker, indicating centrifugal degeneration, seem due to the use of stimuli which were partly submaximal for one of three reasons.

The motor fibers do not run together as a bundle in the center of the sciatic nerve, but rather pass from a loose accumulation of fibers on the dorsal side of the nerve in the proximal stretch to a denser group on the medial-ventral side more distally (Kurkowsky, 1935). With the secondary coil at 13 cms.

and 5° from the vertical, a stimulus is delivered which is not strong enough to excite all the motor fibers unless the electrodes are placed directly on them. It is clear that stimuli which are adequate in one region of the nerve may not be so in another. Further, the eccentric course of the motor fibers makes any twisting of the nerve upon the electrodes of extreme importance. Finally, still with submaximal stimuli, confusing results are obtained when the fiber distribution is altered by branches leaving the main trunk between different regions of stimulation.

These points are illustrated by results on a normal nerve. With stimuli of the strength indicated, the contraction was less with electrodes on the hip region of the nerve than when they were at the knee, while with stronger stimuli the responses from both regions were equal (Fig. 1). This is the result Parker (1933) obtained on a degenerating sciatic nerve. In these experiments,

TABLE 1

Protocol of contraction heights of muscle twitches resulting from stimulation of degenerating frog sciatic cut eight days previous to experiment. Temperature 12°–14°C.

Stimulus strength	Stimulus position					
	Hip		Middle		Knee	
	Over[1]	Under	Over	Under	Over	Under
Weak (13 cm., 70°)	(14)[2]	52	65	30	60	75
Medium (13 cm., 0°)	33	90	83	(78)	(86)	(95)
Strong (9.5 cm.)	100	100	100	100	100	100

[1] Over indicates electrodes were held on top of nerve; under indicates electrodes were held under nerve: in both cases, without regard for true dorso-ventrality of the nerve trunk.

[2] Numbers give contraction height in per cent maximal. Those in parentheses indicate proportionate values interpolated from duplicate experiment.

also, with weak stimuli peculiar responses can be obtained from various nerve levels (and with twisting of the nerve), whereas with adequate stimuli, the responses from all levels of the nerve are the same (Table 1). There is especial danger of using inadequate stimuli on a degenerating nerve because there is a progressive increase in threshold from day to day. (This is independent of the decreased response to a maximal stimulus as more and more fibers become fully inactive.) But when adequate stimuli are used, muscle twitches of constant height result from stimulation at any level of the nerve. Further, the rise in threshold, increase in fatiguability, and falling off of contraction all progress with the duration of degeneration simultaneously along the entire cut nerve.

Current spread from a less excitable central region to a more excitable peripheral one is ruled out by the following experiment: with continued stimulation at H, the muscle response falls to zero due to local nerve fatigue. Stimuli applied at K are still fully effective at this time. With rest, H stimuli recover their full action. Clearly no significant stimulus spread could occur.

Complete loss of indirect excitability occurred about the thirteenth day at 18°–20°C.; about the seventeenth day at 12°–15°C. (Table 2), in the frogs. In the rats (male albino), loss of indirect excitability took place between 50 and 70 hours after operation.

The peculiarities in motor fiber distribution do not significantly influence the oscillograph records. It was found that action potentials declined with time and disappeared simultaneously at all points along the degenerating nerve, as has been clearly shown also by Titeca (1935).

With adequate stimuli, then, and regard for anatomical peculiarities of the nerves, physiological tests show that functional degeneration occurs simultaneously throughout a cut, degenerating, peripheral nerve.

TABLE 2

Loss of indirect excitability of gastrocnemius with increasing period of degeneration of cut sciatic

Temperature	18°–20°C.		12°–15°C.	
Number of frogs	41		19	
Days since cut	+	−	+	−
2– 8	16	0	2	0
9	3	0	2	0
10	2	0		
11	1	0	2	0
12	3	0		
13	2	1	2	0
14	0	3		
15	0	1	2	0
16	0	3	2	0
17–20	0	6	0	7

+ Indicates visible response to stimulation.
− Indicates lack of visible response to stimulation, starting with weak stimuli, and ending with coil distance of 6 cms.

The histological findings also agree, for, as Ranson, Cajal, and others have emphasized, when the region of traumatic degeneration near the plane of section of a peripheral nerve is eliminated from consideration, degeneration of the myelin sheaths proceeds in all parts of the nerve at once. An incomplete histological examination of degenerating nerve, however, can be very misleading. In different fibers at one level, nodes may vary from normal to completely degenerate; but in one individual fiber, though the condition is not the same at all levels, the variation from place to place is much less than that from fiber to fiber at one level. Fig. 2 was taken from a nerve cut four days previously, hence too early for observing progressive degeneration. It is obvious that the nodes of the three figured axones are different—varying from the essentially normal condition in fiber *c* to the moderate degeneration of fiber *a*, shown by the widened node, clearly visible axis cylinder, and beginning myelin globule formation. In like manner, the internodes at the level of the Schwann cell nucleus are respectively normal or fragmented. The signs of degeneration were equally present throughout a 9 mm. length of fiber *a* (teased out), and absent throughout a similar length of *c*.

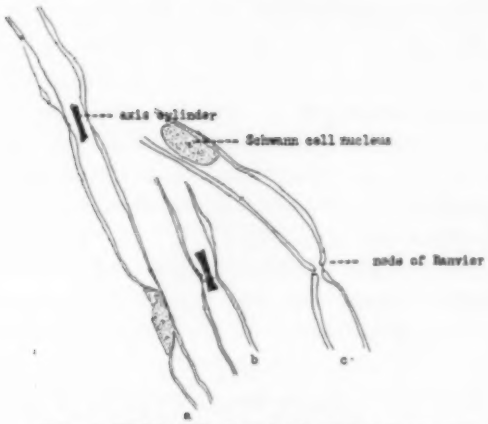

FIG. 2. FNS 4. Left sciatic cut 4 days previously. T = 18°–20°C. At this level, the condition of the nodes is not the same in individual fibers: in fiber a, the nodes are approximately the same throughout 8 mm.—there was no gradation towards the more normal node of fiber c. Fiber b represents a somewhat intermediate stage.

Drawings made with camera lucida on Zeiss microscope, from preparations stained with Sudan III-haematoxylin. In all cases, magnification is 800 ×.

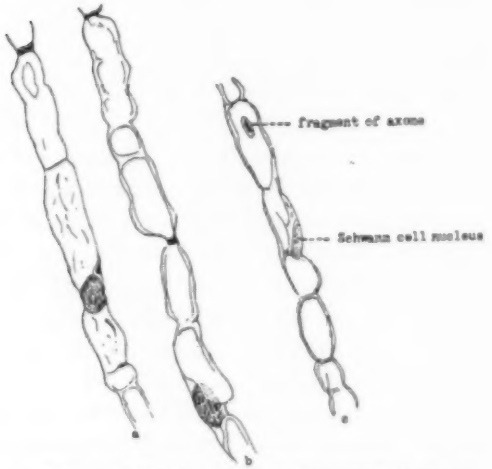

FIG. 3. FOSC 1. Left sciatic cut 13 days previously. T = 18°–20°C. *a* is 4 cms. from cut end; *b* is 5.3 mm. from *a* on the same fiber; *c* is intermediate between the two. It is usually held that the smaller the myelin segments, the more advanced the degeneration. This, then, could not be centrifugal progressive degeneration. Essentially the same condition was found 8.4 to 9 mm. from *a*.

A nerve degenerating at 18°–20°C. for thirteen days, still conducting sufficiently to cause muscle contraction, was examined for a cm. length. 4 cms. from the cut end, as Fig. 3 shows, there is still relative uniformity of degeneration, at a stage much more advanced than that shown in Fig. 2. In no case were fibers found with great fragmentation at one end, and normal appearing segments at the other. It should be emphasized that isolated fields containing different fibers give erroneous impressions unless sufficiently large numbers of fibers are counted. Heinbecker, Bishop, and O'Leary (1932), who made adequate counts, pointed out (p. 7): " . . . the occurrence of undoubted degenerative changes in a variable number of fibers observed in histologic sections is not a true index of the state of the nerve as a whole." This was not considered by Parker and Paine (1934) in their work on the lateral line nerves. The necessity for observing large numbers of fibers on a statistical basis was obviated in this study by teasing fibers and groups of fibers so that they could be followed for comparatively long distances. 300–400 fibers were teased from the frog nerves cut 12–16 days previously, and in no case was progressive degeneration observed: on the contrary, similar degenerative changes were found at widely separated regions of the same fiber.

Discussion

Loss of indirect excitability might be due to a failure at the end plates or to breaks in the functional continuity of the motor axones. If the motor end plates degenerate prematurely so that even when axones still conduct, block occurs at the neuro-myal junction (Tello, 1907; Titeca, 1935; Hołobut and Jałowy, 1936), then no conclusive statements regarding progressive degeneration in nerve can be drawn from muscle twitch experiments. It would be impossible to obtain twitches from stimulation of one nerve region and not from others, as claimed by Parker. If, however, the motor axones degenerate first, or simultaneously with the end plates, then the simultaneous loss of indirect excitability along the nerve trunk is positive evidence of a non-progressive degeneration. Only if axones degenerate first and progressively as described by Bethe (slow progression from the cut end, starting immediately after the injury) or by Parker (progressive degeneration found only between 12 and 16 days after injury) could a centrifugal loss of indirect excitability result. Since both requirements are refuted by the facts presented, this may be excluded.

It is clear that a definitive answer to the question of the progress of degeneration in nerve must rest on analyses within the nerve itself to exclude the end-plate complication. Action potential studies, of nerve function, have been unanimously against progressive degeneration; and histological ones, of nerve structure, predominantly so.

One hypothesis as to degeneration posits that some chemical substance, arising in or near the nucleus, is transmitted to the rest of the nerve fiber, and that it is the lack of this compound (or compounds) which causes degeneration. The "chemical theory" is compatible with either simultaneous or pro-

gressive degeneration, depending on the subsidiary assumptions made; and although Parker and Paine (1934) used it as support for their observation of progressive degeneration in catfish nerve, Bethe (1903), long an adherent of the progressive degeneration theory, rejected the chemical theory for, to his mind, it left no alternative but simultaneous degeneration. This theory was first proposed by Goldscheider in 1894. It has recently been supported and amplified, as against a theory requiring constant passage of trophic impulses, by Cook and Gerard (1931) and Gerard (1932), who observed that increased activity of severed mammalian nerve caused a more rapid degeneration; and similar results were obtained on frog nerve in vitro by Abrams and Gerard (1933). Torrey's (1935) observations on the temperature coefficient of degeneration in frog nerve also supports such an hypothesis. Plausible means for the sufficiently rapid spread of chemicals along nerve fibers have been suggested (Gerard, 1932; Abrams and Gerard, 1933; Parker and Paine, 1934). The nature of the essential substance has been speculated about (Marinesco, 1930, and others), and Minea (1932) has reported a slowing of degenerative processes in rabbit nerve by injections of lecithin and antilipase sera. Certainly the axone, with its independent blood supply, furnishes an admirable test object for studying substitutes for the nuclear influence.

Summary

The cut left sciatic nerves of leopard and wood frogs kept at 18°–20°C. lose the capacity to transmit impulses to their attached gastrocnemii 13–14 days after section. This loss, measured by muscle twitch height, occurs simultaneously throughout the length of the peripheral stump. At 12°–15°, the physiological degeneration is not complete until the seventeenth day after the cut.

Action potentials from these nerves decline and disappear simultaneously throughout the length of the nerve as degeneration progresses.

Histological examination of teased out fibers of degenerating nerves with a modified Sudan III-haematoxylin stain, shows no linearly progressive myelin degeneration.

Discrepant findings by others can be accounted for in terms of the use of stimuli which were inadequate in view of the presence of branches and of the irregular distribution of motor fibers in the frog sciatic, and to failure to eliminate the area of traumatic degeneration at the cut end of the nerve.

These results have been confirmed in rats, where the loss of indirect excitability occurs from 50–70 hours after section. This conforms with the results of Heinbecker, Bishop, and O'Leary on various nerves in cats and monkeys.

I wish to thank Dr. R. W. Gerard for his invaluable suggestions and criticisms. Thanks are also due Mr. F. Offner for his gracious assistance with the electrical apparatus.

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AN OSCILLOGRAPHIC STUDY OF THE CEREBELLO-CEREBRAL RELATIONSHIPS*†

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I. Introduction

Recently the relationship of the cerebellum to the activity of the cerebral cortex has been stressed by experimental and clinical (Walshe, 8) studies. Rossi (6) (confirmed by Bremer, 2) showed that simultaneous stimulation of a lateral lobe of the cerebellum rendered a previously infraliminal stimulus capable of producing a motor response from the contralateral cerebral cortex. Fulton and his associates (1, 5) have shown experimentally the importance of the cortex in the genesis of the cerebellar disturbances. Anatomical studies have indicated the structural basis for these physiological phenomena by demonstrating that the main efferent connection of the cerebellum of primates is with the contralateral motor and premotor areas through thalamic relays. In view of these advances, it seemed probable that, if the cerebellum played an active rôle in the functioning of the cerebral cortex, changes should occur in the action potentials of the motor areas with cerebellar stimulation.

II. Methods of Investigation

The isolated encephalon of the cat, a preparation introduced by Bremer (3), has been used for all the experimental procedures. The preparation is simply made, and once established, no further anaesthetic is necessary. Under ether anaesthesia the posterior neck muscles are scraped from their insertions on the occipital bone to expose the arch of the atlas and the foramen magnum. The intervertebral ligaments and dura between these are incised, bringing into view the lower part of the medulla. With a blunt spatula the exposed medulla is completely transected at approximately the obex. At the time of transection the animal should be deeply anaesthetized to prevent undue shock. Artificial respiration is maintained for the remainder of the operation. A small dose of ephedrine (0.01 gm. per kilo) increases the blood pressure, depressed as the result of lowered vasoconstrictor tone, and insures a good encephalic circulation. The cerebellum, on one or both sides, and the cerebral cortex are exposed in the usual manner and cortical potentials led off by one or two pairs of electrodes (5-6 mm. apart) placed indirectly upon the cortex and recorded after amplification by the Matthews or Dubois oscillograph. Small electrodes connected to the secondary coil of an inductorium, the primary of which is in series with a two volt battery and a key, are used for

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‡ Fellow of the Rockefeller Foundation.

bipolar stimulation of the cerebellar cortex. The frequency of stimulation varies from 12 to 25 break shocks per second. The strength of excitation is generally about that necessary to obtain a motor response from stimulation of the cerebral cortex. Both the stimulating and receiving electrodes are firmly attached to the calvarium by wax, so that slight movements of the head do not introduce an artefact. All experiments were carried out in a completely shielded room; the inductorium was separately shielded.

III. Experimental Results

Faradic stimulation of the cerebellum, especially the cerebellar hemispheres, produces changes in the cortical potentials obtained from the motor areas and to a lesser extent from the parietal and temporal regions. These alterations consist of an increased frequency and amplitude of the cortical waves. Usually the change is striking and not at all to be confused with the unavoidable artefact introduced by spread of potential from the stimulating electrodes. The response usually is initiated by a wave which at times so closely follows the artefact that they seem to be almost synchronous, but which reaches its acme much slower than the spike of the artefact. It is of greater amplitude than the normal cortical waves. Usually smaller secondary waves are present. Their frequency is definitely greater than that of the normal cortical activity, the increase varying between 25–50 per cent. These effects appear immediately without a delay. In some cases they may augment during the first second of stimulation. Following the stimulation the large waves cease immediately, but the cortical activity may not regain its normal rhythm for a half or one second. During this interval the waves are of greater frequency and smaller amplitude than normal. Another feature may superimpose upon this response. During spontaneous sleep, which was frequently the state of the animal, the cortical rhythm is punctuated every few seconds by spontaneous bursts of activity. Cerebellar stimulation may augment the number, intensity and duration of such bursts (Fig. 2 A). Auditory stimuli give rise to similar changes of the cortical potentials led from the temporal lobe (Bremer, 4).

It has not been possible to facilitate the response by repeated stimulation of the cerebellar cortex at small intervals, nor has it been possible to tire or fatigue the response similarly.

These responses to cerebellar excitation may be readily obtained from the motor cortex surrounding the cruciate sulcus and extending posteriorly along the midline. In only three of twenty-one experiments was cerebellar stimulation ineffective, probably due to the poor general condition of the animal. Responses may be obtained to a lesser degree from the parietal and temporal* cortex. Although less distinct and requiring a slightly greater strength of stimulation, such responses present the same characteristics as those obtained from the motor area. Cerebellar stimulation caused no alteration in the po-

* The differences in the resting or normal cortical rhythms of the frontal, parietal and temporal cortex, as pointed out by Kornmüller have been constantly a striking feature.

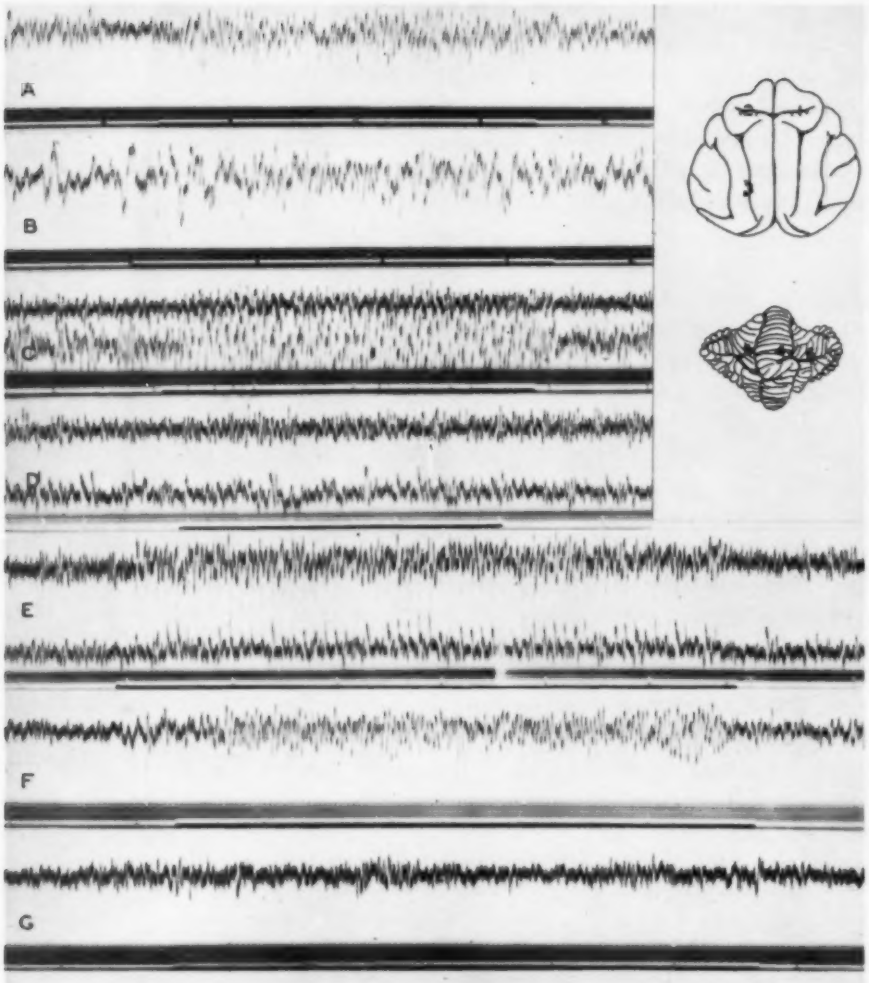

FIG. 1. A and B (cat No. 10) Stimulation of right cerebellar hemisphere with secondary coil of the inductorium at 22.5 cm.

A. Leads from the left cruciate sulcus (point 2).

B. Leads from left parietal cortex (point 3).

C, D and E. (cat No. 11) lead I (upper) from right cruciate sulcus: lead II from left cruciate (points 1, and 2).

C. Stimulation of the right cerebellar hemisphere along the intercrural fissure (secondary coil at 23 cm.).

D. Stimulation of same point as C, but right superior cerebellar peduncle sectioned 15 min. previously (secondary coil at 23 cm.).

E. Stimulation of left cerebellar hemisphere along the intercrural fissure (secondary coil at 25 cm.).

F and G. (cat No. 5) Cortical lead from the left cruciate sulcus (point 2).

F. Stimulation of the lateral portion of the right inferior ansiform lobe (point 6).

G. Stimulation of the right inferior ansiform lobe 3 mm. medial to the point stimulated in A and near the vermis. Secondary coil of the inductorium was set at 26 cm. for F and G, which were taken within 1 min. of each other. (Cont. on p. 19.)

tentials led from the cortex of the occipital lobe other than the spike produced by the spread from the exciting electrodes in the only two cases so studied.

The changes may be markedly diminished or abolished by local application of novocaine or ice to the cerebellar cortex. Under such circumstances although the cortical activity remains normal, cerebellar excitation produces very slight, if any, alteration in the cortical rhythm. The influence of the artefact alone may thus be seen (Fig. 2 B). If the effect of these depressing

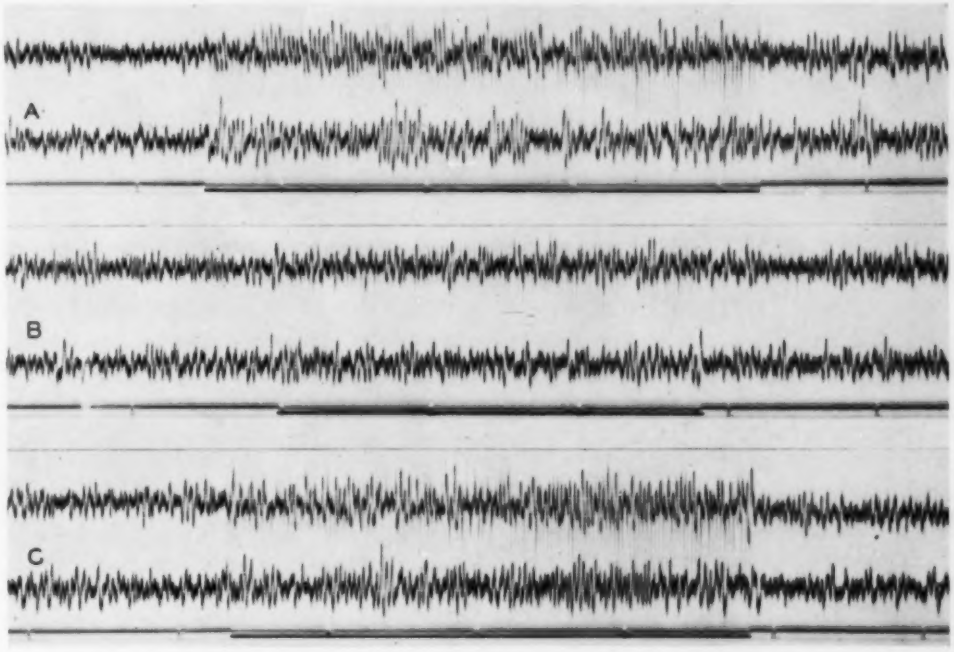

FIG. 2. (cat No. 16) Lead I (upper) from just inferior to the tip of the left cruciate sulcus, and lead II from slightly inferior and posterior to the left coronal sulcus. Stimulation of the right inferior ansiform lobe with the secondary coil of the inductorium at 24 cm.
A. Control record to show the response to stimulation.
B. Record taken after five minutes application of ice to the cerebellar cortex.
C. Record taken eight minutes later to show the response again.

agents is allowed to pass off, stimulation of the cerebellum once more produces marked alterations in the cortical activity (Fig. 2). Following application of 2 per cent novocaine to the cerebellar cortex, strengths of stimulation formerly producing a good response are no longer effective, but stronger excitation may give rise to changes in the cortical potentials. This is not un-

In all records the sensibility of the oscillograph was 20 mm. for 100 uv. The time marker signalled 1 sec. intervals. In a few of the earlier experiments owing to mechanical difficulties, there was a slight delay between the signalling of the closure of the secondary circuit of the inductorium and the onset of excitation. This gives the false impression of a latent period (Fig. 1 F).

expected for such strong stimuli must reach the deep cerebellar nuclei which are not affected by the local anaesthetic.

Abolition of the cortical activity by asphyxiation, readily carried out in the isolated encephalon by discontinuing artificial respiration, prevents a response to cerebellar stimulation. The only effect of such excitation is a series of spikes produced by the spread of potentials from the stimulating electrodes. If artificial respiration is resumed the activity of the cerebral cortex

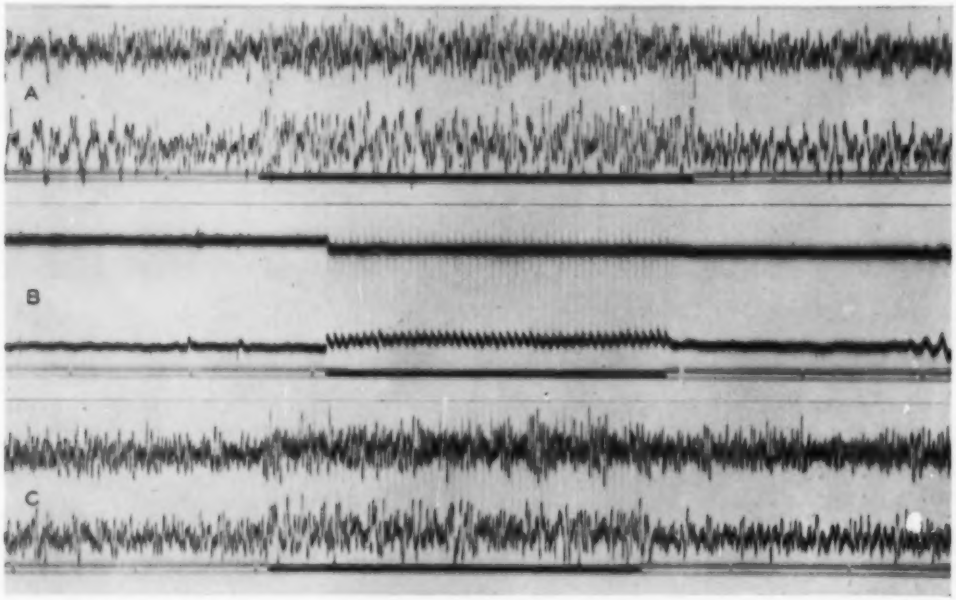

FIG. 3. (cat No. 18) Lead I (upper) from the inferior part of the left cruciate sulcus, lead II from the cortex immediately superior and posterior to the coronal sulcus on the same side. Excitation of the inferior ansiform lobe (right) with the secondary coil of the inductorium at 23 cm.

A. Control record to show the response from these two leads.
B. Record after three minutes asphyxia.
C. Record taken three minutes after B, and two minutes after the resumption of artificial respiration.

rapidly returns and cerebellar stimulation will again produce a response (Fig. 3).

The application of strychnine to the cerebellar cortex has failed in two instances to produce alterations in the cortical activity.

Section of the superior cerebellar peduncle in the two experiments studied has abolished the response obtained from stimulation of the same side of the cerebellum without altering the effect of exciting the opposite hemisphere. In these cases leads were taken simultaneously from both motor areas along the cruciate sulcus. The effect of cerebellar stimulation is thus shown to be not strictly unilateral, a weak response being present in the ipsilateral motor cortex (Fig. 1, C, D, and E).

The response varies with the point of the cerebellar cortex stimulated. Excitation of the vermis does not give any response at times, and at best, it does not give rise to nearly so pronounced changes in the cortical activity as excitation of the cerebellar hemispheres. Within the latter are optimal places for producing a response in any particular point of the cerebral cortex. However, the results of such studies have not been sufficiently constant to warrant a statement regarding cerebellar localization. In general better responses are obtained when the exciting electrodes span the small sulcus between the superior and inferior ansiform lobes (fissura intercruralis) than when either the superior or inferior lobe is stimulated alone.

The method of preparing the animal does not allow coincidental observations on the effect of cerebellar stimulation on the posture of the extremities. Changes in the cortical potentials may occur quite independent of eye movements, which are readily elicited from the anterior part of the cerebellum in this preparation.

IV. Discussion

The increase in the cortical activity subsequent to excitation of the cerebellar hemispheres probably represents a normal function of the cerebellum. Certainly the fact that the changes are abolished when the activity of the cerebellum is arrested by novocainization, or the local application of ice, or its main efferent pathway interrupted by section of the superior cerebellar peduncle is ample evidence that they do not represent artefacts introduced by the potentials of the stimulating electrodes. Because the cortical activity does not appear to be altered by removal of the cerebellar influence by any of these methods it may be assumed that in the cat the cerebellum, while physiologically at rest, does not add a perceptible factor to the cortical rhythm. It is possible that this may be correlated with the fact that hypotonia is not a prominent sign following removal of the cerebellum in this animal. The fact that the cerebellum is able to increase the activity of the motor areas leads to the supposition that the former is exerting a stimulating influence on the cerebral cortex. There is, however, no reason to suppose that this influence is sufficient to produce the specific response of the motor cortex, rather it would appear merely to sensitize the cortex so that it might be activated by a minimal stimulus. In other words it serves to lower the threshold of excitation of the cerebral cortex. Thus one would expect that subthreshold stimuli would produce motor responses when the cerebellum was simultaneously stimulated. This Rossi (6) has shown is precisely what happens.

The fact that the effect is most pronounced in the motor cortex is not surprising in view of previous anatomical (Walker, 7) and physiological (Aring and Fulton, 1) studies. It is possible that the response may be entirely confined to the motor cortex in animals in which the cerebral cytoarchitecture is better differentiated, such as in the monkey, ape and man.

It is probable that both the cerebellar cortex and deep nuclei of the cerebellum take part in the production of this stimulating influence, for although

local application of novocaine abolishes the effect of weak stimuli, stronger ones produce a response. It is likely that this latter effect is due to excitation of the deep cerebellar nuclei. The efferent pathway is by way of the superior cerebellar peduncle to the thalamus. Another neurone then projects to the motor areas of the cerebral cortex. This pathway has been clearly demonstrated anatomically in cat, monkey and anthropoid ape.

That the effect is mainly obtained from stimulation of the neocerebellar parts is not unexpected in view of the anatomical, physiological and clinical evidence that neocerebellar function is largely dependent upon the integrity of the cerebral cortex. Comparative anatomy has taught that the cerebellar hemispheres develop pari passu with the elaboration of the cerebral cortex. Fulton, Liddell and Rioch (5) and Aring and Fulton (1) have shown that cerebellar tremor, essentially a sign of neocerebellar dysfunction is greatly diminished or absent following ablation of the motor cortex.

The neocerebellum is not entirely concerned with the cerebral cortex. Undoubtedly it plays an important rôle in association with the parvicellular part of the red nucleus and the rubroreticular tracts. In ascending phylogeny, however, the neocerebellum is more and more functionally related to the cerebral cortex, especially to the motor and premotor areas.

The significance of this cerebellocerebral relationship is to be found in an analysis of the disturbances resulting from lesions of the cerebellum. Bremer in a recent excellent survey of the subject concludes as follows (2, p. 126): "L'analyse du syndrome de déficit néo-cérébelleux et la considération des connexions cérébello-cérébrales nous amène donc à formuler l'hypothèse que les trois élèments de ce syndrome, l'asthénie volontaire, l'hypotonie musculaire et les anomalies des temps de réaction volontaire, sont l'expression d'une seule et même perturbation fondamentale: le défaut de tonus, l'asthénie, des mécanismes moteurs cortico-bulbaires et cortico-spinaux privés d'une action dynamogénique cérébelleuse." Such a cerebellar action is well confirmed by the present investigation.

The absence of this cerebellar dynamic influence increases the threshold of the cerebral cortex, and in higher primates at the same time releases the peripheral musculature from that slight cortical stimulation which is probably the basis of normal tone. In these circumstances the cerebral cortex must be set into action by an abnormally strong excitation, one which on account of its abnormal strength is apt to produce a response of too great or too little intensity. The lack of tone of the peripheral musculature introduces another disturbing factor. When this is summated by the same abnormal reaction of the antagonists which normally modulate the activity of the agonists, a physiological basis for the ataxia, tremor and dysmetria seen in cerebellar lesions is apparent.

V. Summary

1. Excitation of the cerebellar hemispheres produces a marked increase in the amplitude and frequency of the cortical action potentials from the motor areas of the cat.

2. Section of the superior cerebellar peduncle abolishes the response of the contralateral motor cortex but a slight change in the potentials of the ipsilateral motor cortex may still be elicited.

3. From these experiments it is concluded that the cerebellum especially the neocerebellum exerts a stimulating influence upon the cerebral cortex, which may be the mechanism through which the cerebellum normally maintains a coördinating influence upon volitional movement.

The generous kindness and encouraging criticisms of Professor Fr. Bremer, under whose direction this work has been carried out, have been greatly appreciated. I would also like to thank M. Tirabassi for technical assistance with this research.

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HUMAN BRAIN POTENTIALS DURING THE ONSET OF SLEEP

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WHEN A person goes to sleep, the pattern of his brain potentials alters systematically. Five clearly defined stages have already been described (Loomis, Harvey, and Hobart, 1937) as follows:

A—*interrupted alpha:* the normal waking 10-per-second rhythm dominates the pattern
B—*low voltage:* the alpha rhythm is lost
C—*spindles:* short groups ("spindles") of 14-per-second waves appear and also random "delta"* waves 0.2 second or more in length
D—*spindles plus random:* both types of wave increase in voltage and the delta waves become longer
E—*random:* the 14-per-second waves become inconspicuous, but delta waves continue to increase in voltage and wavelength

We have now investigated the finer details of the *A* and *B* stages, and are able to relate alterations of the electrical pattern of the brain to signals given by the subject which are based upon changes in his state of consciousness. Such a correlation is of great interest from the point of view of psychophysiology, for it unites a subjective with an objective aspect of brain function.

METHOD

The experiments to be described were carried out in the Loomis Laboratory. We employed the amplifiers, the ink-writing oscillographs, the automatic recording drum and accessory apparatus, which have been in use in this laboratory for some time (Loomis, Harvey, and Hobart, 1936). In addition we employed the portable two-channel ink-writing electroencephalograph and associated amplifiers which are in routine use in the Department of Physiology of the Harvard Medical School. These were designed and constructed by Mr. A. M. Grass.† The two sets of instruments on direct comparison proved to be almost identical in their characteristics. The only exception is the electrical filters. The Loomis filters are quite sharply tuned and select one frequency rather specifically from the medley of brain activity. The Harvard filters, on the other hand, are much more broadly tuned‡ and can be legitimately compared to combinations of high-pass and low-pass filters, leaving a band of a third of an octave or more which is passed with relatively

* Following the suggestion by Walter (1936) we employ "delta" as a generic term to designate brain-potential waves whose wavelength is 0.2 second or longer. They may or may not be rhythmic in sequence.

† The work of the Harvard group has been materially aided by a grant from the Josiah Macy, Jr. Foundation.

‡ The higher the frequency to which one of these filters is tuned, the sharper is the tuning. The sharpness may be expressed as the ratio of the frequency at which the amplitude of a sine wave is ½ what it is at the center of the band to the frequency of the center of the band. For 3 per second this ratio is 2.7; for 10 per second, 1.4; and for 14 per second, 1.3.

little distortion. Each type of filter has proved of particular value for particular purposes.

Two signal pens connected in parallel write upon the drum and the tape, respectively. They are connected to a push-button operated by the subject, or to a mercury contact switch driven pneumatically by a rubber bulb held by the subject. (The rubber bulb was introduced to eliminate a rather troublesome electrical artifact which emanated from the push-button and its grounded shield.)

Small metal electrodes were attached in standard positions on the heads of the subjects as follows: (1) Vertex; in the midline directly on the top of the head on a frontal plane through the two auditory meatuses. This point is over or near the sensorimotor area of the legs. (2) Occiput; in the midline about 2 cm. above the inion. This point is over the visual area of the brain. (3) and (4) The right and left mastoid processes or the right and left ear lobes. Points 3 and 4 were used either singly or connected in parallel, as reference electrodes common to all of the recording circuits. We shall speak of electrical activity at the vertex or occiput when we mean, strictly, the electrical potential appearing between vertex or occiput and these ear electrodes. The degree of unlikeness which appears between simultaneous occiput and vertex records shows that it is safe to assume that not more than 10 per cent of the electrical activity is due to potential changes of the ear electrodes, except perhaps in the stage of deep sleep.

Two types of electrode were used in different experiments—(1) a small flat coil of silver wire and (2) a flat drop of solder in which the end of a copper lead-off wire is imbedded. No systematic difference between the results obtained with these two types of electrode could be determined. Much more important than the type of electrode was the state of the subject's skin and the firmness of mechanical contact. Electrical contact was made with Sanborn Electrode Paste and the electrodes were held in place by collodion. It is not difficult to obtain satisfactory electrical and mechanical contact with the scalp without even cutting a hair.

The subject lay comfortably on a bed in a darkened room. A steady noise from an electric fan provided a constant auditory background and masked accidental noises from other parts of the laboratory. The subject was instructed to settle down for an afternoon nap or for the night's sleep, as the case might be, but to signal by squeezing the bulb once whenever he realized that he had just "drifted or floated off" for a moment. The subjective aspect of this "drifting" or "floating" on the borderline of sleep varies with different individuals and will be described in detail below. The subject was also instructed to signal twice if he felt that he had just awakened from "real sleep." Most of our subjects drew a definite distinction between these two experiences. If the subject was still awake after he had given ten or fifteen signals, the experimenter entered the room and obtained from him a description of the subjective experiences indicated by the signals. If he fell asleep as deeply as the *C* stage, it was sometimes necessary to awaken him deliberately.

Results

We have carried out twenty-eight experiments on fourteen different subjects. Three experiments were inconclusive as to any psychophysiological correlation, as the subjects gave no signals. In one case the subject fell immediately asleep without "drifting," and in the other two the subjects were unable to relax sufficently to reach the "drifting" stage. Five other experiments were qualitatively positive, but are not considered in detail because of technical differences or inadequacies which make it impossible to compare them in detail with the main series. In the remaining twenty experiments satisfactory records and signals from eleven subjects were obtained. For purposes of exposition, we shall disregard for the moment the signals from the subject and first describe the typical onset of sleep in terms of electrical activity of the brain.

The onset of sleep. We can distinguish several fairly well-defined steps in the approach and onset of sleep. These steps are not to be confused with the stages *A*, *B*, *C*, etc., of Loomis, Harvey, and Hobart, but represent a more refined analysis of stages *A* and *B*.

As a subject "settles down" his alpha waves may first increase slightly in voltage and regularity, but in subjects who have a steady alpha rhythm, a modulation of the alpha waves soon appears, i.e., the alpha waves systematically increase and decrease in voltage. The period of this modulation is several seconds and is sometimes quite rhythmical. The maximal amplitude of the alpha waves also tends to be reduced. Many individuals show a similar modulation of the alpha waves even when fully awake, and in such an individual the trains of alpha waves become shorter and the voltage lower as he becomes drowsy.

The second step is complete interruption of the alpha rhythm for periods of 1 to 5 seconds. Sometimes the alpha activity does not disappear entirely during these gaps, but the waves become small and irregular both in shape and frequency (Fig. 1B and C). A sharply tuned filter fails to respond to them.

The third step is that the interruptions of alpha activity become longer, although at the end of each gap the alpha waves return quite suddenly, usually with their normal maximal amplitude. At this stage an increase in voltage of the longer, random, delta waves can first be clearly identified. The delta waves appear during the gaps in alpha activity. Most individuals show some slow waves of low voltage at all times as a slight irregularity of the baseline, but in the stage in question slow waves appear singly or in groups of three or four, sometimes quite rhythmically at a frequency of 4 or 5 a second, with a voltage of approximately 50 microvolts (Fig. 1D). The delta waves tend to be larger and more easily identified at the vertex than at the occiput. The changes in alpha activity, on the other hand, are most clearly discerned in the occipital record.

Some individuals have little or no alpha activity in the waking state, but have instead many shorter, sharper waves of 50 to 60 msec. in wavelength which appear irregularly or in brief trains. When they are regular enough to

constitute a definite frequency it is usually 17 to 20 per second (Fig. 2B). These waves are clearly quicker than alpha waves and they do not disappear when the eyes are opened, yet they are slower than the waves which generally have been designated as "beta" waves, namely, those with frequencies above 20 per second (Berger, 1929, 1930, 1934). In their general characteristics they seem more nearly akin to beta than to alpha waves. They are more prominent at the vertex than at the occiput. A generic term for these waves would be convenient, but it seems wiser to defer assigning a Greek letter or other

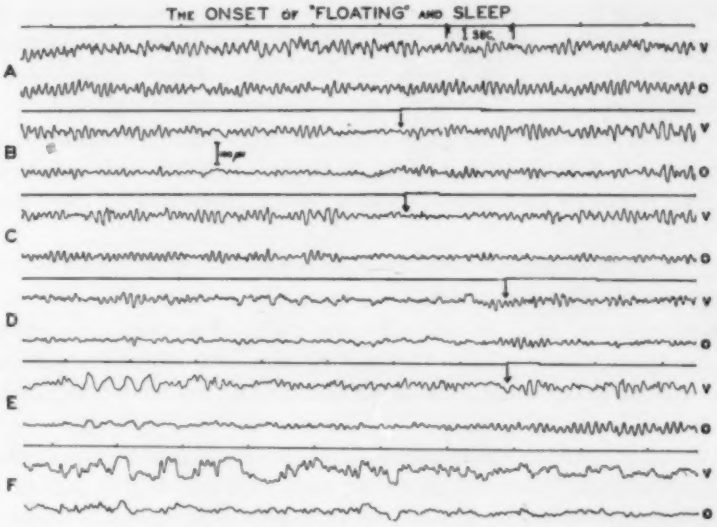

FIG. 1. Six sections from the record of a subject going to sleep and signaling "floating." The upper line of each record shows potential changes at the vertex (V), the lower, at the occiput (O), with reference to the ears. Upward deflection means O or V negative to ears. Time scale and amplification are constant throughout as shown in the figure. A: Normal record of the subject awake. B, C, D, E: "Floating" with signals from the subject on rousing. Drosiness is increasing throughout this series. Note in B that the alpha waves disappear at the occiput before they disappear at the vertex. Note that in C the subject's signal precedes the return of alpha waves. F: Real sleep; entering the *C* stage, with waves at 14-per-second and 12-per-second in addition to large delta waves. The largest delta waves appear square-topped because the limit of the linear range of the recording system has been reached. The actual voltage of these waves is at least 150 microvolts.

specific designation to them until more is learned of their significance and relationships. In this paper we shall refer to them as "quick" waves, and reserve "beta" for frequencies above 20 per second and wavelengths of 50 msec. and shorter.

Three individuals in our series, whose waking records are dominated by these quick waves, show the usual increase in delta waves with the onset of sleep. As drowsiness increases, there is a general reduction in voltage and usually also in the average frequency of the quick waves. The quick waves do not cease entirely, and, inasmuch as they are often quite irregular even in

the waking state, there is no abrupt loss of regularity such as we find in the typical alpha waves.

The fourth step in the onset of sleep shows an increase in the wavelength of the delta waves which appear during the gaps of alpha activity. Alpha waves, when they appear at all, show a slower frequency than the individual's normal waking rate (Fig. 2C). The slowing usually amounts to 10 per cent, and may be as much as 20 per cent. The slowing is not uniform, however, for immediately following a gap, when the waves first return, they are accelerated by as much as 10 per cent above the waking frequency and then progressively slow down to 9 or $8\frac{1}{2}$ per second before the next interruption. The temporary acceleration is particularly evident if the subject has given a signal and it is very similar to the acceleration which often occurs when the subject opens his eyes for a few seconds and then closes them again. *The slowing of the alpha rhythm below its normal frequency is a characteristic phenomenon associated with the approach of real sleep*, although it may not be very evident if an individual goes directly into deep sleep without lingering in the intermediate "floating" stage.

The fifth step is characterized by the complete loss of alpha waves and by the appearance of delta waves of 150 microvolts or more (Fig. 1F). If the delta waves are rhythmic, as is frequently the case, the most characteristic frequency is 4 per second or a little slower. We shall see later from the subjective reports of the subjects that this stage should be regarded as probably real sleep.

The next stage, which is certainly sleep, corresponds to the *C* stage of the original classification (Loomis, Harvey, and Hobart, 1937) and is identified by the appearance of characteristic brief trains ("spindles") of waves at 14 per second and 50 microvolts or more in voltage (Figs. 1F, 2F and 2G). In this stage there is a still further increase in the average voltage of the delta waves and also an increase in their average wavelength.

If we compare the preceding description of the alpha waves with the original classification of the *A*, *B*, and *C* stages of sleep, it appears that the *A* and *B* stages alternate with one another for a time as the subject goes to sleep. This description is incomplete, however, for, although there is a fluctuation between alpha activity and absence of alpha activity (which we shall find is correlated with temporary subjective changes in the state of consciousness of the subject), there can nevertheless be traced a general trend underlying these briefer fluctuations. This trend appears as a lengthening of the periods of absence of alpha activity, as a progressive slowing of the alpha rhythm, and also as an increase in voltage and average wavelength of the delta waves when they appear. The general trend is associated with increasing drowsiness of the subject. On this general trend is superimposed a series of fluctuations of some other factor, which is expressed by the intermittent outbursts of alpha activity.

As a rule, alpha activity and delta activity are inversely related, that is, delta activity tends to appear only when alpha activity is suppressed. This is

true in general, but it is important to note that the rule is not invariable. Particularly in the very early stages, before the alpha rhythm is significantly slowed, the alpha waves may disappear for a few seconds without any measurable increase in delta activity. Furthermore, the alpha waves may disappear

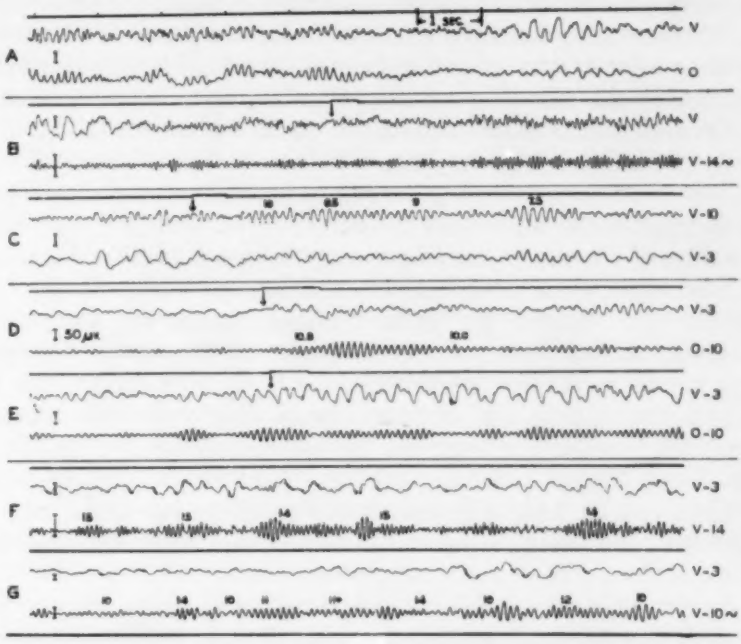

FIG. 2. Brain potentials from vertex (V) or occiput (O) referred to the ears. Upward deflection = scalp negative. Broadly tuned filters used in all except A and upper line of B. Frequency of filters shown by numerals at extreme right. Voltage calibrations at left, 50 μv in all cases. When tuned filter is used calibration refers to peak-to-peak voltage of a sine wave of frequency matching the tuning of the filter.

A: Unfiltered, showing unusually prompt appearance of delta waves in a brief "float" (or nap?).

B: End of a "float," with subject's signal at arrow showing return of "quick" 18-per-second waves in a subject with very few alpha waves. Lower line shows the same potentials taken simultaneously through a 14-per-second filter. The frequency of the waves is approximately 18 per second.

C: Return of alpha waves after a "float," showing variability and slowing of alpha rhythm in the very drowsy state. Alpha frequency indicated on record. The next "float" begins just after the sequence of 7.5-per-second alpha waves. Both records from the vertex. Upper line filtered for alpha; lower line for delta.

D and E: Ends of two "floats" from the record of the same subject. D: The usual return of alpha waves shown in lower line, which is occipital record filtered for alphas. E: Shows unusual delta activity appearing at the vertex. Alpha waves at the occiput continue unaffected by it. This delta episode continued more than 30 seconds. The subject signaled during the delta activity as shown, and believed himself to be fully conscious throughout.

F and G: Records from the vertex of a single subject during sleep. Upper line filtered for deltas; lower line for 14 per second and 10 per second. F: Typical 14-cycle "spindles." G: Irregular slowing of 14-cycle waves, giving rapid shifts of frequency between 14 per second and 10 per second. Frequency count shown on the record. Note reduced amplification of G as compared with F. Also in both cases lower line is taken at twice the sensitivity of the upper line.

in one region—the occiput, for example—while they continue for a few seconds at the vertex, and *vice versa*. Still more important is the occasional appearance of fairly high delta waves running as a continuous background on which the alpha waves are superimposed, or a transient episode of great delta activity at the vertex while the alpha activity continues smoothly at the occiput. We may note immediately that, in the three such episodes of which we have clear records, the subject did not report sleep but believed himself to be conscious. In the case illustrated in Fig. 2E the subject reported unusual kinesthetic and somasthetic sensations, as if he were slightly dizzy and starting downward in a fast elevator. Whatever the significance of this report may be, it is clear that various parts of the brain do not always show simultaneous changes in the alpha and the delta waves.

Correlation of Changes in the Electroencephalogram with the Signals from the Subject. The subjects in these experiments signaled whenever they felt they had momentarily "floated" or "drifted" off or experienced any other clearly defined change in the state of consciousness. These signals correlated to a surprising degree with the alterations in the brain potentials (Figs. 1 and 2). The relation was clearest and most precise in those subjects whose standard waking record was largely occupied with alpha waves. Six of our subjects had such "high alpha" records, showing the alpha rhythm 70 per cent or more of the time. In 9 experiments these 6 subjects signaled "have floated" or "have slept" 165 times. All but 6 of these signals were preceded by definite depressions of the alpha waves which lasted from 1.5 to 30 or 40 seconds. The records showed only 39 equally clear depressions of alpha waves which were not signaled. One subject signaled correctly 20 consecutive depressions, and two others had consecutive runs of 10 or more. The minimal duration of a depression which was necessary for a subject to give his signal varied somewhat from one individual to another. One subject consistently signaled gaps as brief as 1.5 second, others required gaps of 4 or 5 seconds, but for each the minimal duration was quite consistent. The data of Table 1, based on two subjects, are broadly typical of the whole group, and also illustrate the characteristic prolongation of the "floats" as sleep approached.

The signal was usually given immediately after the return of alpha waves (Figs. 1B, D; 2C, D, E). The latency of the signal following the first reappearance of alpha waves varied from zero to as much as 5 seconds, and is more or less characteristic of the particular subject. Occasionally the signal was given just *before* the alpha waves returned (Fig. 1C). This is a point of considerable theoretical interest, as it suggests that a subject may be able to realize that he has "floated" even when his alpha waves are still absent and that the waves may return because the subject rouses himself further by the act of signaling. In order to test this point it will be necessary to carry out similar experiments while obtaining records simultaneously from many parts of the brain, for the reappearance of alpha waves, like their disappearance, is not necessarily simultaneous at all points on the cortex. The latencies in Table 1 are all calculated on the basis of the return of alpha waves at the occiput, where these waves are usually most prominent.

In those cases in which the delta waves reached 150 microvolts and persisted for half a minute or more, the subject frequently signaled "real sleep" when he next awoke. Two subjects did not identify any intermediate stage between waking and real sleep, and almost all of the changes which occurred in their records involved the appearance of large delta waves for half a minute or more. Sometimes a subject who showed this type of change in the record would neglect to signal "real sleep" on waking, but state subsequently that he realized later that he had made a mistake and should have signaled "real sleep" rather than mere "floating." The situation suggests that the ability to discriminate between "floating" and sleep becomes relatively depressed when sleep actually occurs. Occasionally a period of one or two minutes of unquestionable sleep passed entirely unsignaled. This agrees with our experience in other experiments in which such changes have appeared in the records and in which the subjects have denied having fallen asleep. Akin to this is the situation toward the end of an experiment when the subject is asleep most of the time and often fails to signal when alpha waves appear for a few seconds on the record. In this state the subject apparently does not arouse himself sufficiently to give the signal, and we have not included this part of the experiment in reckoning our scores. If we consider that even in the early "floating" stage the subject is in an extremely drowsy state, perhaps only semiconscious, it is surprising that our subjects actually attained an overall score of 75-per-cent accuracy of signaling depressions of alpha activity.

TABLE 1

Subject	Signals	Average time between signals	Average duration of depression of alpha waves before signals	Average time from return of alpha waves to signal
A	1– 5	16.9 sec.	2.9 sec.	0.2 sec.
	6–10	12.1 sec.	4.1 sec.	0.2 sec.
	11–15	17.8 sec.	7.8 sec.	0.4 sec.
	16–20 (sleep)	20.5 sec.	13.5 sec.	0.3 sec.
B	1–3	30.2 sec.	6.2 sec.	2.4 sec.
	4–6	37.8 sec.	10.4 sec.	2.6 sec.
	7–9 (sleep)	36.2 sec.	22.7 sec.	1.1 sec.

Failures to signal the changes perfectly occurred for several reasons besides extreme drowsiness. One reason was that on the first trial the subjects did not always sink deeply enough toward sleep. They did not attain the necessary condition for "floating," but, being anxious to cooperate, began signaling too soon, not waiting for the correct end-point. The failure was essentially the selection of the wrong subjective end-point. It is significant, however, that among all of the subjects who gave any signals at all only one failed to reach the proper end-point at one of his later trials; and even the one whose experiment we class as a failure was not entirely negative in his correlations toward the end of his second trial. According to his own statements, however, he was still shiting his end-point from time to time in an endeavor to find what we call the "floating" stage.

Occasionally the subject fluctuated very rapidly, according to his record, between a state of waking and a state of "floating," and under such conditions he frequently failed to signal all of the fluctuations. The period of such fluctuations was often as short as 5 seconds. Furthermore when the fluctuations are very rapid, the contrast between the sections of the record is often not great. The subjects expressed the greatest uncertainty concerning the subjective transitions on those very occasions when the record itself showed no sharp contrasts. Sometimes also there were very slow gradual transitions from one state to the other which apparently escaped the notice of the subject. It is significant that the very conditions which make judgment of end-points difficult on the record seemed to be correlated with a similar lack of clear definition and clear transition in the subject's own experience.

The Subjective Experiences. Two of the ten subjects in the successful experiments reported only "real sleep," and these two actually showed characteristic sleep patterns in 7 out of 12 alterations of pattern which were signaled. The first two alterations in each record were less clear than those which followed, but delta waves of at least 70 microvolts were visible in every case. The shortest period of delta activity was 10 seconds. These are more profound changes than our other subjects showed in their early "floats."

Our two youngest subjects (21 and 13 yrs.) gave no adequate description of their experiences. Their records passed quite rapidly into the characteristic sleeping pattern with only two and four intermediate "floats" (or naps?), respectively, but signals were given immediately after the alterations in every case.

The remaining six subjects who gave signals related to the changes in their potential patterns all agreed on two points—(1) that they would not call the early episodes "real sleep" but an intermediate stage, and (2) that during the episodes which they signaled there had been a depression of awareness or consciousness. The depression involved the awareness of immediate external stimuli (e.g., sounds, contact of the bed-clothes, etc.), or of self-consciousness, awareness of the experimental situation, etc. One of them compared the state to that of "nodding" or "dozing" during a lecture or sermon, and others agreed to the aptness of the comparison. Beyond these common points they gave the greatest variety of descriptions, such as:

(1) "These things are practically dreams, but I am awake enough to catch them." (99)*

(2) "No dreams or visual fantasies. Mind a blank. Noises no longer noticed." (12)

(3) "Unexpected visual fantasies are my end-point." (98)

(4) "My thoughts wandered or floated unexpectedly." (15)

(5) "Drifting of thoughts. Definite kinesthetic sensation of being suddenly brought upright at the end." (95)

* The figures in the parentheses following these descriptions are the "alpha indices" of the respective subjects, i.e., the percentage of the time occupied by alpha waves in his waking record under standard conditions (Davis and Davis, 1936; Saul, Davis, and Davis, in press.)

(6) "Pleasant sense of numbness, of dizziness, of being nothing at all." (72) These six spontaneous characterizations cover the senses of hearing, touch, equilibrium, and kinesthesia; and include thought, visual fantasy and dreams. They also include emphatic denials of dreams and visual fantasies.

We have no evidence relating dreams to specific changes in the record. The fantasies of the "floating" stage merge imperceptibly into dreams, and we have many unequivocal reports of dreams which must have occurred during the *B* stage, for the subjects never went beyond the *B* stage in those particular naps. One subject was awakened abruptly from the *C* stage by a knock on the door. He reported that he had just been dreaming and had awakened spontaneously, but had forgotten the content of the dream. Only 3 seconds elapsed from his last large "spindle" of 14-per-second waves (which preceded the knock) to his own signal indicating that he was awake, so that it seems quite safe to refer the dream to the *C* stage. Dreaming can therefore occur in both *B* and *C* stages. Concerning *D* and *E* we have as yet no evidence.

Discussion and Incidental Observations

In the reports of our subjects as to their subjective experience during the times when alpha waves were depressed in their records, no single sense modality is uniquely involved. We therefore cannot assume that the alpha waves are depressed in the "floating" stage because of *visual* activity in the form of fantasy, analogous to opening the eyes. In fact, "floating" seems rather to involve a depression of cortical activity, while opening the eyes and also those emotional states such as startle, "puzzlement," apprehension, etc., which suppress the alpha waves, are clearly forms of stimulation.

Inspection of the records leads to the conclusion that alpha activity may be reduced in two distinct ways. In one situation, as in "floating," the waves cease, simply *diminishing in voltage* to zero. They return again abruptly, then fade out once more, but, as they come and go, there is also, with the approach of real sleep, a general *slowing of the alpha rhythm* to 8 or even to 7 (cf. Durup and Fessard, 1936; Jasper, 1936). The slowing is most noticeable when the subject goes to sleep slowly with many "floats" in and out. Whenever the frequency falls to 7 or 6.5 per second the waves become irregular and disorganized and the subject passes off into another "float" or into real sleep. The behavior of the alpha waves resembles the slowing and disorganization of alpha waves in hypoglycemia described by Hoagland, Rubin, and Cameron (1936).

The 14-per-second waves which are so characteristic of sleep appear at about the stage when the last few recognizable alpha waves have been depressed to a frequency of approximately 7 per second. In a few instances in our records it appears that 7-per-second waves which are presumably slowed alpha waves have broken up into two groups which beat alternately with one another, thus generating a rather irregular 14-per-second frequency. The possibility of such an apparent doubling of frequency has been suggested in another connection by Rheinberger and Jasper (1937). This mechanism,

however, will not account for the genesis of the 14-per-second "spindles" in general, for the latter appear quite characteristically in the records of individuals who have no clearly marked alpha waves at any time. Also the 14-per-second waves are higher in voltage than the alpha waves at this stage of sleep.

The alpha waves are not the only ones which are progressively slowed with the onset of sleep. The quick (20-per-second) waves are similarly affected; in the individuals in whom the quick waves are prominent enough to be studied easily the groups of 14-per-second waves appear strongly when the average frequency of the quick waves has fallen to approximately 14 per second. This observation, although pointing to a genetic connection between the quick waves and the 14-per-second waves (cf. Jasper, 1937), offers no clue as to why the 14-per-second waves should reach a voltage higher than that exhibited by the quick waves at other frequencies. The frequency does not remain stable at 14 per second, but may oscillate between 14 and 10 per second or thereabouts (Fig. 2G). The "spindles" of 14-per-second waves have been identified because here seems to be a maximum of voltage and perhaps a somewhat greater stability of frequency in each train of waves.

Waves at approximately 10 per second may appear during sleep (cf. Blake and Gerard, 1937), but their frequency is seldom as regular as the waking alpha rhythm. Also a subject who has fallen asleep and lost his alpha waves for a time may show them again for a few seconds without signaling that he is awake, and they may be elicited regularly by stimuli which fail to arouse the sleeper. The pattern of brain potentials may change, and the subject may shift his position in bed, but when awakened may have no memory of the stimulus. The function of memory is certainly depressed. If the subject does give a signal in this state, its latency, with respect either to the stimulus or to the appearance of alpha waves, is unusually long—often many seconds, and giving the signal often involves great subjective effort. Whether or not we regard the subject as "asleep" under these conditions (when the alpha waves appear) is a question of definition which we shall leave open for the present.

One of our subjects always gave strong regular 10-per-second waves from vertex, occiput, and forehead nearly continuously while deeply asleep. There is no doubt as to the depth of sleep in this case. The 10-per-second waves appeared only in the *C* stage of 14-per-second waves. Frequencies of 10 and 14 per second often appeared simultaneously in the record. This subject gives such "alpha" waves *only* when soundly asleep. Her waking record is dominated by quick 20-per-second waves, and relatively few sharp irregular alpha waves appear. (The alpha index of this subject is 15.) It is a question whether or not her regular well-rounded 10-per-second waves in sleep represent the same cell-groups and mechanisms as the ordinary waking alpha rhythm. Her sleeping 10-per-second waves are strongest at the vertex instead of at the occiput, but this is also true for the waking alpha rhythm in about 2 per cent of our normal subjects. Obviously the test of opening the eyes could not be

tried in sleep! We believe that the sleeping 10-per-second waves in general are more closely akin to the 14-per-second waves of the spindles and to the "quick" 18- or 20-per-second waking waves than they are to the waking alpha rhythm. In sleep the 14-per-second and 10-per-second frequencies are not sharply differentiated. Many trains at 12 per second can be identified (See Fig. 2G). It is at 14 per second, however, that the highest voltages and greatest regularity are usually attained. In all subjects the sleeping 10-per-second waves, like the 14-per-second waves, are more prominent at vertex than at occiput, and they are equally strong in individuals with many and with few waking alpha waves.

Is "falling asleep" a unitary function or event? Our observations suggest that it is not. Different functions, such as sensory awareness, memory, self-consciousness, continuity of logical thought, latency of response to a stimulus and alterations in the pattern of brain potentials all go in parallel in a general way, but there are exceptions to every rule. Different functions may be depressed in different sequence and to different degrees in different subjects and on different occasions. Only the general progress of depression remains constant. We have pointed out that the changes in the pattern of brain potentials need not occur simultaneously in different parts of the brain. Only if we choose to define sleep in terms of response to a particular stimulus or of a particular change in the potential record from a particular area of the cortex—only then can a "moment of falling asleep" be precisely defined. Otherwise the problem is just as vague and difficult as that of determining the exact moment of death.

In terms of potential patterns the index which seems *most nearly* to reflect the "depth of sleep" is the frequency and voltage of the slow, random "delta" waves. Blake and Gerard (1937) have pointed out this general parallelism and it is implicit in the classification of stages of sleep cited in the opening paragraph of this paper. Our present observations show that the delta activity begins to increase both in voltage and in average wavelength at the stage of the earliest subjective "floating" or transition into sleep. The increase in voltage and wavelength appears to continue progressively as the physiological depression of the nervous system which we call sleep becomes deeper. It is probably no accident that most forms of mental disorder except the convulsive varieties have been reported as showing "slow waves" of one kind or another in those cases in which any difference from the normal could be detected (Berger, 1932, 1933; Gibbs, 1937; Walter, 1937; Jasper, 1937). We have confirmed this general relationship in a series of observations which will be reported in detail elsewhere.

The abruptness with which a subject's record can change from a high-alpha waking pattern to a "light sleep" record with clear delta waves (cf. Fig. 2A) raises an important practical point for clinical electroencephalography. Before we conclude that a low-alpha or a high-delta pattern is due to mental disorder, brain tumor, or other lesion of the brain, we must be certain that the patient was awake when the record was obtained and that he did not

momentarily "float off" in light sleep. Records must be carefully evaluated in terms of the state of the patient. Measurements of the amount of alpha activity are particularly subject to error from drowsiness, which may partially depress the alpha waves long before actual sleep occurs. Absence of drowsiness must be rigorously enforced as one of the necessary standard conditions for such measurements.

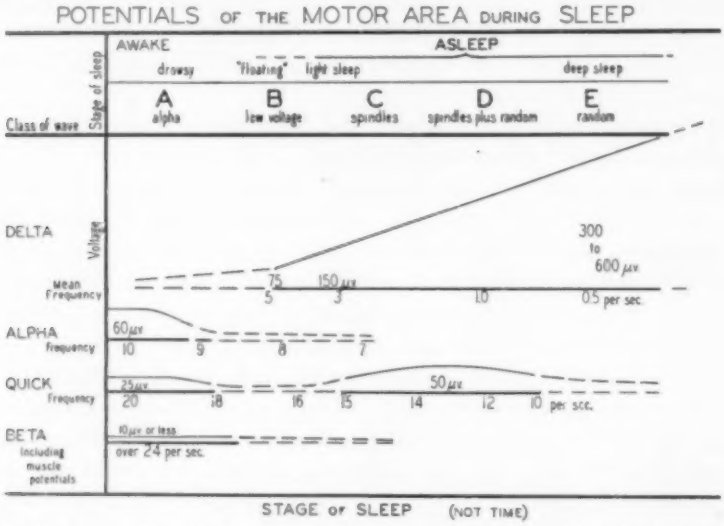

FIG. 3. In the upper line the stages of sleep are characterized by the subject's reports; in the next line, according to the classification of Loomis, Harvey, and Hobart (1937).

The classes of waves are defined by the values given for their frequencies. The delta waves sometimes have no clear frequency but appear as isolated waves, and strictly should be defined by wavelength rather than frequency. In sleep they tend to be fairly rhythmic.

The height of each curve above its own base-line indicates the most characteristic maximal voltage for that class of wave at the corresponding stage. Note that the voltage scale for delta is half that of the other classes.

Broken lines indicate that at the corresponding stage of sleep the frequency of the waves in question becomes irregular or that its appearance is very intermittent, or its identification uncertain.

The frequency of the alpha waves is the most definite and constant. The others vary from moment to moment by as much as 25 per cent. This may or may not indicate corresponding shifts in the "depth of sleep."

The chart describes the potentials from the motor area referred to the ears. The corresponding chart for the visual area is similar except for lower voltage of the delta and the "quick" classes of waves. Some individuals show very little alpha voltage, even when awake, particularly in the motor area.

The following chart (Fig. 3) summarizes graphically the typical behavior in sleep of the various components of the brain-potential pattern. It is to be regarded as tentative and highly schematic, since the various components are not necessarily as closely correlated with one another as this graphic representation implies, i.e., the dominant frequency of quick waves need not be exactly double the alpha frequency, although this is often the case. Broken lines signify variability of behavior or intermittent appearance of the corre-

sponding class of wave. It is important to note that the horizontal dimension does not represent time. A subject frequently shifts back and forth from one stage of sleep to another, sometimes quite rapidly and erratically.

Summary

Brain potentials were recorded from subjects while they were going to sleep. Alterations in the pattern were related to the state of consciousness of the subject by means of signals given spontaneously by the subjects (Fig. 1).

Subjects who have a well-developed alpha (10-per-second) rhythm when awake often showed repeated depressions or loss of alpha waves while going to sleep. Just after such a depression the subject typically signaled that he had "floated" or "drifted off" for a moment. Slow "delta" waves, 0.2 to 0.3 second in duration, usually appeared during the depression of alpha waves. Subjects who have few or no alpha waves showed a corresponding but less clearly marked depression of their "quick" (15- to 20-per-second) waves, and the same appearance of "delta" waves.

Nine of our ten subjects gave signals which correlated clearly with alterations in their brain-potential records. The "floating" state of consciousness always involves a loss of awareness for immediate external stimuli. Some subjects, but not all, also describe visual fantasies, kinesthetic sensations, interruptions of logical thought, etc.

"Real sleep" was regularly acknowledged when slow waves (recorded from the vertex) had reached 150 μv and persisted for half a minute. The appearance of "spindles" of 14-per-second waves is a sure sign of real sleep.

Dreams may occur in the low-voltage, *B* stage and also in the 14-per-second, *C* stage.

Alterations in the alpha and delta waves are not always simultaneous in different parts of the brain. We cannot define exactly the moment of going to sleep or the moment of awakening.

In the clinical study of brain potentials the drowsy state must be strictly avoided because of the similarity of the patterns of very early sleep to those described for many abnormal conditions.

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THE BEHAVIOR OF CATS FOLLOWING BILATERAL REMOVAL OF THE ROSTRAL PORTION OF THE CEREBRAL HEMISPHERES*

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TWO RECENT studies of the effects of bilateral removal of the frontal lobes of the cerebral cortex of the cat have been at considerable variance as to the symptoms obtained. Langworthy and Kolb ('35) have observed an exaggeration in motor activity in their animals and make no mention of a pronounced plasticity in the decorticate extensor hypertonus. Barris ('37), on the other hand, has reported a profound loss of motor initiative together with a hypertonus of an extremely plastic type suggestive of catalepsy and his comparison of this cataleptic condition with that investigated in this laboratory after brain stem lesions has led us to attempt to verify his observations. We have, therefore, subjected a series of cats to bilateral one stage removal of the frontal lobes.

METHODS

The animals were operated under nembutal in the manner employed by Barris ('37). The skin was incised, the frontal sinuses opened, the nasofrontal ducts plugged with bone wax and the interior of the sinuses sponged with merthiolate. The anterior portion of the calvarium was then removed, the dura incised and all large available vessels were tied and sectioned. The cerebral hemispheres anterior to a plane in the region of the ansate sulci were removed on each side, hemorrhage was stopped, the subcutaneous tissue sutured and the skin closed with clips. Three animals were so active on the first and second postoperative days that they knocked the clips out of the anterior part of the medial longitudinal skin incision. These were killed immediately and in most of the remaining eight animals a transverse skin incision between the ears was employed and the animals were kept in a large cage during the first few postoperative days. Intraperitoneal injections of normal saline solution were administered daily until the animals ate.

The survival times of these eight animals were as follows: One cat suddenly became prostrate and died on the sixth postoperative day, possibly from embolism. One animal, in good health, widely opened its skin incision as a result of excessive activity during confinement for a test of temperature regulation on the sixth postoperative day, and was killed. Four to six weeks after operation, the remaining six animals were utilized in terminal experiments in which the excitability of the preoptic region and hypothalamus was tested. The results of the latter study, together with the information obtained regarding temperature regulation in these animals, will be reported in con-

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nection with other work. The following description is concerned with the animals' general symptomology.

Results

Activity, postural defects, tonus. In light of the loss of motor initiative which has been claimed for them, these animals exhibited a remarkable amount of activity usually from the first or second postoperative day onward. This was perhaps not abnormal since we have seen very restless normal cats which have been just as active. The activity was usually confined to an almost continuous walking about, but two of the animals trotted across the room on the third and fourth postoperative days. Though in motion most of the time when out of their cages for observation, the animals often stopped to look at other cats and seemed perfectly capable of inhibiting their activity. They would not at first turn aside to avoid obstacles, however, and with considerable difficulty would scramble over the rungs of a low stool in their path, or when walking across a table would walk over the edge. They showed a pronounced disposition to follow the observer duplicating every turn made by him.

At a time varying between the first and second postoperative week two of the animals lost this over-activity and disposition to follow and became about as quiet as the average laboratory cat. It was found at autopsy that these two animals suffered smaller cortical ablations than their fellows who continued to exhibit the above tendencies throughout their survival periods.

The loss of postural reactions, which the exacting study of Bard ('33) has shown to be dependent on the sensori-motor region involved in these ablations, made the animal's progress awkward during the first postoperative days, but improvement was rapid and subsequently postural defects were chiefly apparent when an animal was at rest, or starting or stopping motion, or when making a turn. These defects were usually manifest as a slipping of one or more of the limbs from under the body, forward, to the side or backward, or as a stepping on the dorsum of the foot. In two instances the fore limbs were crossed. Running or scrambling movements appeared when the animals were restrained from moving forward, the animals often becoming very excited.

It was quite impossible to pose the animals in any position.

An extensor hypertonus of the limbs was apparent in the standing posture and gait of two animals on the first postoperative day, but was usually present only when the limbs were freed of participation in standing or walking. It was seen best when the animal was suspended ventral side down either by the chin and tail or in a hammock, and then was marked and exhibited no plasticity. Usually in the course of the first postoperative week the animals became restless in the hammock, swaying the vertebral axis from side to side and making running movements of small amplitude. In most cases an extensor hypertonus of the limbs was apparent also when the animals were on their backs in a trough during the first two or three postoperative days, and some

of the animals would lie quietly in this position during the first postoperative week. Others, however, had to be restrained in the trough from the first postoperative day and righted themselves as soon as released, at first by a ventroflexion of the trunk and later by turning to the side. There was little or no plasticity in the extensor hypertonus in any of the animals when on their backs and it was impossible to pose any of them in the trough.

Feeding, gastro-intestinal tract. With the exception of one cat which ate meat on the first postoperative day and drank milk on the second, the animals would not eat meat spontaneously until the fourth to sixth postoperative day and would not drink milk until the sixth to eighth day. All would chew and swallow meat placed in their mouths two or three days before they began to eat spontaneously. In eating meat some of the animals licked the meat into their mouths, while others made lunging bites and swallowed the mouthful obtained without chewing. They would indiscriminately bite or lick the edges of the pan. All of the animals lapped milk, often lapping the edge of the pan or the air, or dipping the nose far into the milk. When feeding, the animals frequently made treading or pawing movements with the forelimbs, placed the forefeet in the dish, and sometimes purred or growled. They appeared very hungry.

The same two cats which lost their over-activity and disposition to follow quickly acquired better eating habits than their fellows. The animal which ate from the first postoperative day was not a member of this group, however.

The stomach and intestines of each animal were examined at autopsy, but the results do not compare favorably with those of Mettler, Spindler, Mettler and Combs ('36) who found gastric hyperemia and ulceration following bilateral removal of the frontal lobes in the cat. A single ulcer was found in the pyloric region of the stomach of the animal which died on the sixth postoperative day. This consisted of an area of mucosal erosion about 2 mm. in diameter with slightly elevated and pinkish margins. We question its relationship to removal of the frontal lobes, however, for the stomach and intestines of all the other animals were normal.

Emotional behavior. We cannot agree with Barris ('37) that there is any more than a very transient impairment in the emotional reactivity of these animals. The response to pinching the tail was uniformly weaker than normal during the first, second and third postoperative days. It regained a normal vigor during the fourth to sixth days, however, and on pinching the tail the animals cried loudly, spit, circled and in some instances attempted to strike the observer's hand.

Three of the cats exhibited an aversion to their fellows from the third postoperative day onward. One of these animals, when another cat approached her on the third postoperative day, rolled onto her side, extended the limbs in front of the fore part of the body, with the digits spread and claws bared, and repeatedly struck with the uppermost forelimb; the ears were retracted, the pupils widely dilated, the cat spit several times and for a short time afterward growled intermittently.

The animals showed every indication of marked emotion when in a room with barking dogs in cages, but unfortunately this was not tried until most of the animals were in their first or second week of survival, and the earliest test was on the sixth postoperative day. In this instance the cat faced the dog which was barking the loudest and remained in the center of the room, with

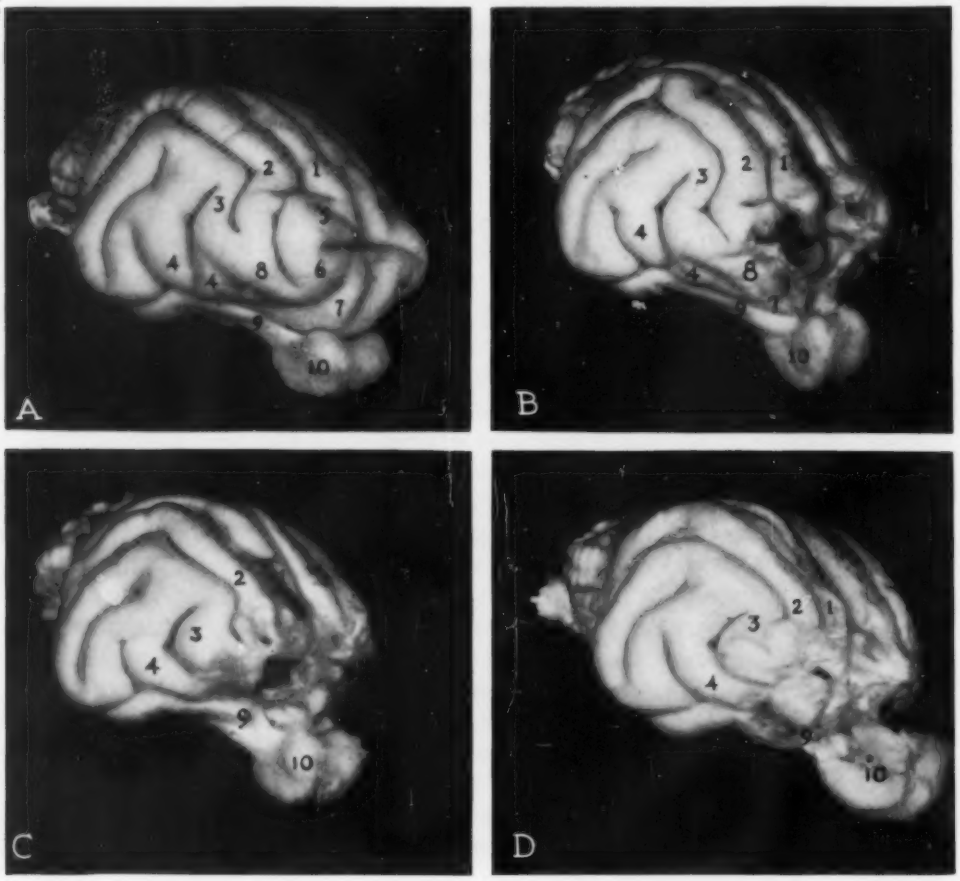

FIG. 1. Photographs of brains of: A, normal cat; B, Cat 1; C, Cat 2; D, Cat 3. The numerals have the following significance: 1, lateral gyrus; 2, middle suprasylvian gyrus; 3, anterior ectosylvian gyrus; 4, anterior sylvian gyrus; 5, posterior sigmoid gyrus; 6, anterior sigmoid gyrus; 7, frontal gyrus; 8, coronal gyrus; 9, olfactory stalk; 10, olfactory bulb.

its limbs extended, back arched, and tail vertically upright. The hair on the back and tail was maximally erected and the pupils maximally dilated. The cat's repeated, explosive spitting could be heard above the noise of the dogs. The cats with longer survival times exhibited just as normally vigorous pilomotor, pupillary and facio-vocal activity but instead of assuming the Halloween posture just described, crouched and retracted the forequarters

and head, and two of the animals subsequently turned and ran out of the room.

With the possible exception, however, of the three cases which were antagonistic toward their fellows, a trait occasionally present in the normal cat, these animals have not impressed us as possessing the intense emotional hyper-excitability seen in the completely decorticate cat (Bard, '28; Bard and Rioch, '37).

The animals showed a pronounced affection toward the observer. They circled, arched and rubbed themselves against the observer when petted, often purring and making treading movements with the forelimbs, and when studying the animals it was difficult to take notes with the cats on the table as they would not stay away from the observer.

Extent of ablation. In all of the animals the posterior sigmoid, anterior sigmoid and most of the coronal and frontal gyri (terminology after Papez, '29) were removed bilaterally. In the two animals which recovered from an initial over-activity and tendency to follow, and which regained essentially normal eating habits, this was the extent of the area ablated, as is seen in the photograph of the brain of Cat 1, shown in Fig. 1B. The extent of ablation can be determined by a comparison with the normal brain shown in Fig. 1A.

In the remaining four animals the ablation was slightly more extensive so that the anterior ends of the lateral, middle suprasylvian and anterior ectosylvian gyri were removed and all of the coronal gyri and the anterior half to two-thirds of the anterior sylvian gyri were bilaterally ablated. Even the most ventral portions of the frontal gyri were either removed or disconnected from more caudal regions. In three of these animals the olfactory tracts were considerably injured on one or both sides, as in Cat 3, whose brain is shown in Fig. 1D, but in one animal, Cat 2, whose brain is shown in Fig. 1C, they appeared intact and it was this cat which ate from the first postoperative day. All four of these animals, however, showed persistent impairments in feeding habits, a deficit which has been attributed by Langworthy and Kolb ('35) to removal of the electrically excitable cortical field for masticatory and lapping movements located in the region of the rostral end of the anterior sylvian gyrus (Magoun, Ranson and Fisher, '33; Ward and Clark, '35; Tower, '36). The present results, as far as they go, support this interpretation, but isolated removal of this field might be expected to yield more critical information.

Summary

A description is given of the pronounced activity, loss of postural reactions, extensor hypertonus without plasticity, impairment in feeding and retained emotional behavior of cats following bilateral one stage removal of the frontal lobes of the cerebral cortex.

This description appears essentially identical with that presented by Langworthy and Kolb ('35). The cataleptic phenomena described by Barris ('37) were not observed.

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FORCED CIRCLING IN MONKEYS FOLLOWING LESIONS OF THE FRONTAL LOBES*

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PRIMATES from which the cortex of one cerebral hemisphere has been removed circle in walking toward the side of the lesion; such animals also show contralateral hemiparesis together with deviation of head and eyes toward the side of the lesion. With all types of progression there is rotatory movement which appears to be involuntary and purposeless and becomes accentuated under emotional stimuli such as rage, fear, or the sight of food. Deviation of head and eyes, and circling occur in hemidecorticate cats and dogs, as well as in subhuman primates. After lesions of the frontal lobes, Hitzig (16) observed the same symptoms in dogs and attributed the phenomena to paralysis of the trunk muscles of one side. In 1895 Bianchi (3) noted that monkeys with "prefrontal" ablations circle toward the side of the lesion, due, he thought, to visual and to "intellectual "disturbances. In man also conjugate deviation of the head and eyes appears after certain cortical lesions, and many focal epileptic attacks begin with turning of head and eyes (10).

In the following experiments an attempt has been made to analyze in the monkey (*Macaca mulatta*) the physiological factors involved in circling, and to localize the cortical area responsible for this symptom.

METHODS

In the present study lesions of area 8 were made in 12 normal rhesus monkeys (*Macaca mulatta*). In addition observations were made on a large number of monkeys, with lesions elsewhere in the cortex which had been operated on for other purposes. Excisions of cortical areas were made under aseptic technique and the animals were observed subsequently over a period of several months.

PRELIMINARY CORTICAL ABLATIONS

In attempting to determine the region of the brain responsible for circling and head turning observations were made on animals with lesions involving various cortical areas. As these studies have an important bearing upon area 8 ablations to be described below, they may be briefly summarized.

Hemidecortication. The symptoms following hemidecortication in the monkey are well known (Hitzig, 16; Karplus and Kreidl, 19). A profound contralateral hemiparesis develops immediately together with a sensory deficit and hemianopia. The phases of recovery are also predictable; during the *first week* power returns to such an extent that the animal is usually able to sit and stand, and even to walk and climb awkwardly. The paretic extremities, at first flaccid, begin to show spasticity at about the third day and tend then to be held in greater extension than the normal limbs. They are less sensitive to touch and to pain on the affected side than on the normal, and the sensory deficit is also evident in progression for the animals tend to "lose" the extremities, which become tangled in awk-

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ward postures. Forced grasping is prominent and tendon reflexes, at first decreased, tend ultimately to become exaggerated on the paretic side. Deviation of the head and eyes and curving of the body are marked as soon as the animals regain their feet; any emotion, excitement, fear, or rage accentuates the head deviation and tendency to circle. Although the head and eyes are usually held toward the side of the lesion, they are frequently turned in the opposite direction when the animal is not under stress, and immediately after operation the eyes can be fully deviated in both directions.

By the end of the *first month* improvement is considerable, but movement and posture in the paretic limbs are not normal, for there is persistent spasticity with hyperactive tendon reflexes; the sensory deficit to touch and pain is less marked. No fine movements are performed with the paretic hand or foot, and fingers and toes can not be used individually. All purposeful movements are executed either by the normal side alone, or by the normal extremities first, followed and assisted by the paretic members. At this stage deviation of the head and eyes is less marked than after operation, but is still conspicuous. The animal tends to look toward the normal side and to circle in this direction, but at times is able to move forward in a straight line.

Recovery in both motor and sensory spheres continues slowly but steadily after this for at least the first six months. Motor deficit, hemianopia and a tendency to circle have been observed to be present for a year; indeed the symptoms probably persist indefinitely, for the hemidecorticate macaque reaches a permanent motor status which can never be mistaken for normal.

In such animals the circling has been attributed to visual abnormality (Karplus and Kreidl, 19). Hemianopia, together with deviation of the eyes to the "seeing" side might produce a turning of the animal toward the objects seen. However several of these animals in which circling movements were present were blindfolded without altering motor performance. On one, a hemidecortication was performed some time after the opposite occipital lobe had been ablated. This blind animal also circled.

Frontal lobe. Isolated extirpation of the frontal lobe in monkeys (areas 4, 6, 8, 9, 10, 11 and 12) produces similar forced turning with deviation of head and eyes. These symptoms however are neither as extreme nor as enduring as in the hemidecorticate preparations and recovery from the hemiparesis also is quicker and more complete. During the first postoperative week the monkey without one frontal lobe recovers sufficiently to walk, climb and run adequately, although all movements on the paretic side show clumsiness and incoördination, spasticity and hyperextension. The fingers and toes are not used for fine movements at this stage. Forced circling is conspicuous as is deviation of the head and eyes; these last symptoms are present for several weeks but become less noticeable during this interval. A tendency to rotate when excited persists for months, being detectable long after deviation of the eyes or head has entirely disappeared.

The "visual" defect present following frontal lobe ablation will be described later in the discussion of the effects of lesions of area 8.

Areas 4 and 6. Ablation of the motor and premotor areas (areas 4 and 6, upper part, Fig. 1) together or in series, is followed, as is well known, by contralateral motor paresis (11). It has been suggested that circling movements occur because of weakness of the extremities of one side; however, these animals show no circling even at the height of their motor paresis. After isolated ablation of face and neck fields (areas 4 and 6, lower part), the resultant imbalance of the neck musculature does not cause forced circling and the head and eyes remain in the mid-line in spite of noticeable facial weakness.

Ablation of the remaining parts of the frontal lobe exclusive of areas 4 and 6 (i.e., areas 8, 9, 10, 11 and 12), is always accompanied by deviation of the head and eyes, and by forced circling *without attendant paresis of the face and limbs.* When various of the frontal association areas were then ablated singly and seriatim it developed that removal of fields 9, 10, 11 and 12 caused no one of the three symptoms, and that motor performance following such ablation could not be differentiated from that of a normal animal.

Other cortical areas. Removal of an occipital lobe is followed by hemianopia which differs from the visual defect of frontal lesions in that it is a permanent object-vision blindness. Such hemianopia is not accompanied by forced turning. There are times when these animals turn, because, as is obvious in watching them, they can see only to one side, and must therefore look only in that direction. The performance, however, is quite different from the regular circling movements of which follow ablation of a frontal lobe with area 8 removed. In true hemianopia turning is only occasional and is clearly visual in origin; it is never purposeless.

The effect of removal of the other centers for eye movements (Graham Brown, 12) has not as yet been investigated fully. In a few animals from which the parietal lobe had been removed and in which there was no hemianopia, deviation of the head and eyes has been noted, but without the forced and purposeless turning movements.

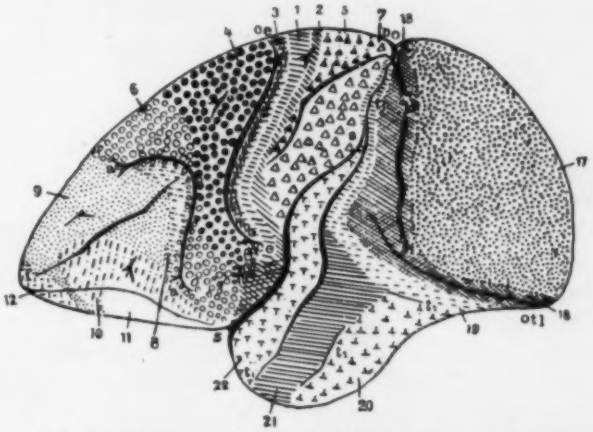

FIG. 1. Brodmann's cytoarchitectural map of monkey's brain (cercopitheque). Extirpation of the region indicated here as area 8 leads to forced circling syndrome in the macaque.

ABLATION OF AREA 8

Ablation of a small area inside the curvature of the arcuate sulcus of the macaque (Fig. 2) roughly corresponding to area 8 of Brodmann (Fig. 1) is invariably followed by a definite syndrome which includes turning of head and eyes and circling. Area 8 as described by Brodmann in cercopitheque lies within the arcuate sulcus along its anterior lip (Fig. 1). Stimulation of this region produces movement of the eyes—usually conjugate—horizontal and away from the side stimulated, and is followed after an interval by turning of the head as well. Mesial to the arcuate sulcus in an area corresponding with the junction of areas 6 and 9, eye and head movements can also be obtained by stimulation. Here the head movement is most often primary and followed by that of the eyes. Widening of the pupils is also produced on stimulation here (Graham Brown, 12; Beevor and Horsley, 2; Leyton and Sherrington, 21; Wilbur Smith, 26). The mesial limb of the arcuate sulcus in the macaque is very deep and extends both mesially under area 6 and caudally deep to area 4. It is variable as to exact shape and depth as are all the cortical sulci in this species. Lesions of area 6 on the mesial side of the sulcus produce no turning

of the head and no eye symptoms, unless area 8 as well is inadvertently damaged.

Unilateral ablation. Unilateral excision of the region anterior and lateral to the arcuate sulcus (i.e., area 8) is followed by deviation of the head and eyes and circling progression toward the side of the lesion. The symptoms are

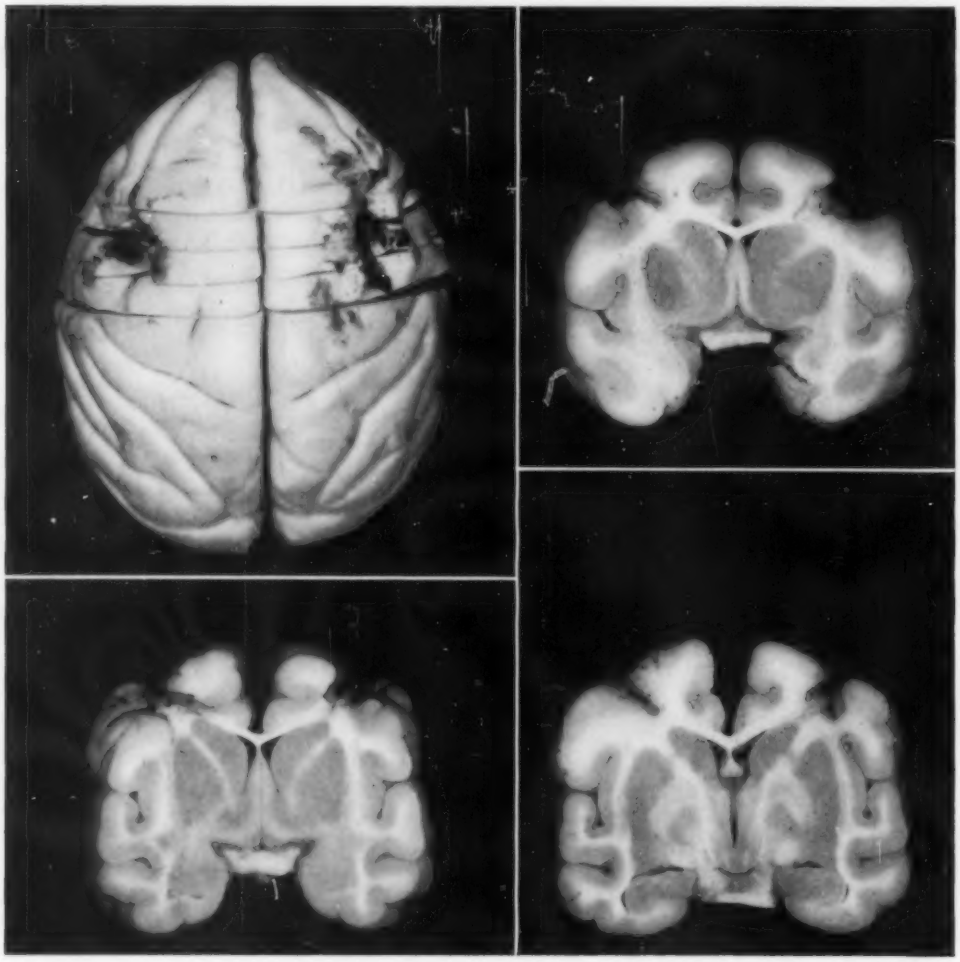

FIG. 2. Brain of a macaque (*M. mulatta*) after bilateral extirpation of area 8 showing extent of lesion into depths of sulcus, but without injury to caudate sulcus.

extreme during the first two or three postoperative days and all motor progression is accompanied by circling and turning of the body. During the succeeding two or three weeks the eye and head turning gradually becomes less and then disappears. A tendency to circle toward the side of the lesion persists for several months. However, this syndrome occurs only if area 8 is removed in its entirety, including all the gray matter in the depths of the arcu-

ate sulcus. Removal of the superficial cortical tissue produces only a fleeting trace of the syndrome.

The term "forced circling" has been used to describe this performance both because the animals are unable to move except in circles, and also because they seem to move more but with less purpose than the normal animals; thus, any emotional stimulus incites great motor activity and consequent revolving of the animal. When the conjugate deviation and the circling have disappeared the purposeless activity continues and the animals are restless, easily excited and hyperactive. At no time do they show any abnormal posture or paresis of the extremities.

In addition to the above symptoms these macaques present a transient condition which is difficult to distinguish from hemianopia. That is, they apparently do not see in the contralateral visual fields. They pay no attention to food placed in this side of their cage, they do not respond by blinking to threats made in this field and when small bits of food are brought into the field of vision from this side no response occurs until the mid-line of vision is approached. This defect disappears gradually, but persists for a time after the disappearance of conjugate deviation. The duration and intensity of the abnormality are both affected by lesions elsewhere in the frontal lobe, for the deficit lasts longer and is more pronounced following frontal lobe extirpation than after ablation of area 8 alone.

Bilateral ablation. If area 8 is removed first from one side and then from the other the same syndrome develops; after the symptoms from the first ablation become less marked, removal of the second area will temporarily reverse the direction of head and eye deviation, and of circling movements.

When area 8 is ablated from *both sides simultaneously*, or one shortly after the other, the picture which develops is striking, and quite different from that seen following any other type of discrete cortical extirpation. Immediately following operation such animals show all the motor symptoms seen after bilateral extirpation of the frontal association areas plus area 8. There is no paresis or postural deficit but the animal sits motionless at first. The head is sunk between the shoulders, and the gaze fixed and straight ahead; blinking is infrequent, movements of the eyes are almost absent. Eye movements in either direction are possible, for the eyes tend to follow an object, but always return to a fixed central stare. Such animals sometimes appear to be blind, although they follow moving objects and although visual stimuli produce frequent rage reactions. They walk into objects, forcefully striking their heads against the side of the cage. They will reach for and grasp any type of object offered, but then do nothing with it. It is difficult to feed them for they do not seem to know what to do with food. This inability to appreciate objects in the normal manner seems to be due to tactile as well as to visual disturbances for many times things held in the hand are not recognized.

During the first week these animals become more alert and begin to distinguish between objects seen. After a period of a few weeks they become nearly normal except that they continue to have a "wooden" expression and

fixed gaze. Circling movements in bilateral preparations occur and may take place in either direction, the animals often turn one way and then reverse and turn the other for a time. The circling is not as prominent as it is in the unilateral preparations, but the stereotypy and the forced character of all movements are conspicuous and there develops a restless and purposeless behavior in which the general activity seems to be increased.

Discussion

Discrete ablation of area 8 in the monkey is thus followed by a definite syndrome which is composed of two groups of symptoms: first a change in motor activity which consists of involuntary circling, appearing in the absence of postural or paretic changes in the extremities; and second, a defect in the visual apparatus consisting, when the lesion is unilateral, in: (a) a deviation of the eyes toward the lesion, and (b) a contralateral defect in vision. The two groups of symptoms are always part of the same syndrome for neither occurs in animals in which the other has not also existed. The symptom complex seems to be identical with that described by previous authors in animals from which all tissue rostral to the motor areas has been removed (Bianchi, 4), although in the present series only the small portion of these areas known as area 8 is injured.

Histological identification of this cortical area is at present difficult. Grossly it is well defined in the macaque (Fig. 2) as the region lying within the arcuate sulcus—that is, anterior and lateral to the sulcus, and roughly corresponding to the area 8 demarcated by Brodmann for the cercopitheque. The histological structure of this area is transitional from the agranular motor cortex of area 6 to the granular cortex of the true frontal association area 9 (von Economo, 27; Campbell, 6).

The cytoarchitectural maps of both Mauss (22) and Brodmann (5) have confined the limits of area 8 within the arcuate sulcus in the monkey. In the higher apes and in man, however, this area extends to the mid-line, rostral to area 6 (Brodmann, 5; von Economo, 27; Foerster, 10), and Hines has stated that in the macaque as well a strip of tissue which is cytoarchitecturally indistinguishable from area 8 of Brodmann runs mesially from the arcuate sulcus to the mid-line (13).

The physiological evidence is also that this region extends to the mid-line in macaque, anthropoid, and man, for eye movements may be elicited from stimulation of all of this strip of tissue although their character changes in the different parts, much as in areas 6 and 4 specific regions subserve different muscle groups for limbs. On the other hand removal of the mesial part of this strip designated to area 6 is followed by no appreciable alteration in head or eye performance. The forced circling appears only when the more lateral part now designated as 8 has been damaged.

Motor defect. In 1868 J.-L. Prévost published a Paris thesis entitled: "De la déviation conjugée des yeux et de la tête dans certains cas d'hémiplégie" (24). In it he cites 58 human cases of hemiplegia, which showed deviation of

the head and eyes. The lesions were widely distributed within the central nervous system and were for the most part diffuse—four only being limited to cerebral cortex, and only one to the frontal lobe. He also cites the scanty experimental literature concerning deviation of the head and eyes in animals; symptoms infrequently noted at that time following cerebral hemispherectomy and remarks on the circling movements which accompany this deviation.

In 1874 Hitzig (15), and in 1875 Ferrier (7) first elicited movements of the eyes from stimulation of the cerebral cortex. The region of the sigmoid gyrus of the dog (Hitzig) and the "base of the superior frontal convolution" in the monkey (Ferrier, 8) were the regions from which such movements were produced. In human beings deviation of the head and eyes have long been known to accompany hemiparesis, and to be a part of some attacks of Jacksonian epilepsy. In 1926 Foerster (9) was able to stimulate a series of human brains under local anesthesia, and then reported conjugate turning of the eyes from stimulation of areas 8a, 8α and 8β, and, from the region more mesial (area 6aβ), adversive turning of head, eyes and body.

In the lower primates, the monkey or anthropoid, functional differentiation here, as in other regions of the cortex, is not so discrete as it is in man. After stimulation of more lateral cortical eye centers of the monkey (area 8) eye movement is primary, and followed often by head. Repeated stimulation of the anterior portion of area 6, on the other hand, will in the same animal, tend to give primary head movement, which is followed by movement of the eyes. It is rare, however, in these animals that movement of the head can be produced without eye movement as well.

Activity. Greater specificity of cortical localization in the human is further demonstrated by the fact that increase in motor activity has never been correlated with head and eye deviation in man whereas in the monkey after lesions of area 8 one is accompanied by the other. In man, hyperactivity is known to be a factor in certain types of "mental" disorders such as the overactivity of the manic, or the restlessness of some post-encephalitic patients, and these changes have been attributed to changes in the frontal lobe, but no more discrete localization has been possible.

In animals, restlessness and an increase of purposeless activity following bilateral frontal lesions are described by many authors (Hitzig, 16; Bianchi, 4). Jacobsen (17) has found it in lesions limited to the frontal association areas in monkeys; and recently Richter and Hines (25) have observed hyperactivity following both prefrontal and striatal lesions in monkeys. They find that in pure cortical lesions removal of area 9 alone produces maximum hyperactivity, although some appears following lesion of area 8 as well, but that the greatest increase is seen only when the tip of the caudate nucleus is damaged. They do not record associated turning movements. At present, in our studies, there is evidence to indicate in corroboration of Richter and Hines, that there is greater increase in activity following extirpation of all the frontal association areas together with area 8, than of area 8 alone, and that this may occur

without injury to the caudate. Further investigation of this point is in progress. The head and eye symptoms which follow discrete lesions of area 8 are also pronounced and more enduring when other parts of the frontal lobe are removed in addition to area 8 (18). The motor eye fields of parietal and occipital lobe (Graham Brown, 12), probably also play a part in the intensity of this reaction.

"Visual" defect. The nature of the disturbance in response to visual stimuli as a component of this syndrome is difficult to explain. The head and eye deviation may be produced by removal of normal motor innervation to the muscles of the head and eyes and may thus be analogous to the paresis induced by removal of a specific part of the true motor areas 4 and 6. In this respect area 8 is a region elaborating complex motor performance for the head as does area 6 for the extremities. The unilateral visual defect is more difficult to analyse. It is of such a nature that objects in the contralateral field of vision are disregarded. Since, however, the defect is transient, and, when bilaterally present, does not result in blindness, it cannot be a defect in the afferent visual apparatus as in true hemianopia due to occipital lesions. Similarly, it cannot be merely an *apparent* visual defect due to loss of motor power in eye muscles, since eye movements are present in all directions at a time when the visual defect also exists. Unilateral absence of the blink response to threat at a time when other types of lid closure are bilaterally equal also precludes pure motor deficit. The defect obviously lies in the cortical connections between sensory and motor regions, and it can only be described at present as a lack of recognition of or an inability to respond to afferent visual stimuli.

There are a number of earlier descriptions of "hemianopia" related to lesions of the frontal lobe. In 1895 Bianchi, extirpating one frontal area in monkeys, described a visual defect which he recognized as transient, and which he thought to be a hemianopia. The dogs of Minkowski (23) and of Hitzig (16) exhibited unilateral visual defects after lesions in one sigmoid gyrus. L. Bard (1) in 1904 described such an abnormality occurring in association with conjugate turning of the eyes and head in hemiplegic humans. These patients, like our monkeys, did not blink in response to threat in the defective eye field. Bard believed that the defect was sensory.

The bilateral syndrome. The striking alterations in general performance of animals after bilateral removal of area 8 is in every respect like that following ablation of all the frontal lobe areas exclusive of 4 and 6. Bianchi marvels at his monkeys in this state, and at the great "intellectual" deficit which they display as they sit motionless and apparently dazed following operation, and then evolve a purposeless overactivity and tendency to rage. The same emotional instability has appeared to a marked degree in our animals.

We have as yet no evidence as to the relationship of changes in activity to caudate injury such as have been described by Richter and Hines (25), for, in the present series, the caudate nucleus was not damaged. In view of the physiological and direct anatomical connections which exist between area 8 and the striate nuclei (Hirasawa and Kato, 14), it is pertinent to draw at-

tention to the similarity in symptoms between the monkey deprived of area 8 and the human post-encephalitic in whom striatal disease is present. Restlessness, "drivenness," immobility of facial expression and noticeable diminution of blinking and of eye movements are symptoms which may be common to both conditions.

It is of interest also that much of the "stuporous" behavior described in frontal animals is undoubtedly due to disorder of the components discussed in this paper. Clearly the bilateral production of this visual deficit might result in the tendency to sit still, to walk slowly, to bump into objects and to blink seldom in response to threat. Thus also the circling of the unilaterally ablated preparation which appears in relation to deviation of the eyes and head, and which is of a forced and purposeless nature may, in the bilateral preparation, result in the constantly increasing forced overactivity of the first postoperative months.

Summary

1. The unilateral and bilateral ablation of area 8 in monkeys is followed by a characteristic syndrome similar to that produced by removal of the entire frontal lobe, rostral to area 6 (areas 8, 9, 10, 11 and 12).

2. A deviation of the head and eyes toward the side of the lesion is produced by lesions of area 8, which becomes less marked during the first postoperative weeks. A tendency to turn the head in this direction persists much longer.

3. Forced purposeless circling movements appear coincident with head and eye deviation. They also diminish in intensity but persist as hyperactivity for as long as a year.

4. A "visual" defect is present contralateral to the lesion which is not a hemianopia but which has to do with inability to respond to visual stimuli.

5. The picture of "intellectual" deficit described by Bianchi following bilateral frontal lobectomy may be attributed to the alterations in vision and in motor performance just described.

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THE REPRESENTATION OF RESPIRATORY MOVEMENTS IN THE CEREBRAL CORTEX

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I. Introduction

Most previous studies on the control of respiration by the central nervous system have centered mainly around the myelencephalic "respiratory center." In contrast to the exact knowledge which we possess concerning the manner in which breathing is regulated by the "respiratory center," little is known concerning the rôle of the higher parts of the brain in the phenomenon of respiration. The fact that man can voluntarily alter the rate and duration of either one or both of the respiratory phases, that he can change the respiratory rhythm and can even voluntarily arrest respiration for a certain length of time indicates that the cerebral cortex exerts an influence on respiratory movements. In addition, it is an observable fact that mammals in general, in the waking state, modify their respirations in various ways and it seems possible that these modifications are influenced by impulses from the cerebral cortex. If one assumes that the cortex is not equipotential in its ability to alter breathing, then certain areas ought to be found that are able to produce reasonably constant alterations of the respiratory movements when electrically stimulated under uniform experimental conditions, but the reports of previous investigators have been so at variance with one another that one is unable to determine from them precisely what areas of the cortex are concerned.

HISTORICAL NOTE

Lepine, in a communication to the Société de Biologie in 1875, is reported to have stated that excitation of the anterior part of the cerebral hemispheres in the dog slows and even arrests respiration. Since this report investigators have published data which indicate that alterations in breathing can be obtained from widely separated parts of the cortex. Bochefontaine (1876) obtained irregular and inconstant alterations from stimulation of "those points that have an action on movements of different parts of the body." François-Franck (1887) contended that respiratory alterations could be obtained only from the sigmoid gyrus in the dog and cat and that no correlation existed between the point stimulated and the resultant response; weak stimuli were found to produce acceleration, strong stimuli a slowing. Danilewsky (1875) in three instances obtained slowing or arrest of breathing in the cat and dog from stimulation of an area in the suprasylvian gyrus. Unverricht (1888, 1897) using dogs was unable to confirm the findings of Danilewsky, but he located an area in the ectosylvian gyrus from which slowing or arrest of respiration was obtained. Preobraschenski (1890) confirmed Unverricht's findings in the dog, and in the cat he located two cortical respiratory areas; one near the rostral end of the suprasylvian sulcus produced arrest of the thorax in expiration, the other a short distance caudad produced arrest in inspiration. Bechterew (1911) from his work and that of his associates confirmed Preobraschenski's findings in regard to the area for expiratory arrest in the cat. In the dog he found two areas which responded with slowing or arrest of respiration, one in the rostral part of the suprasylvian gyrus from which arrest in expiration was obtained, and another near the end of the sulcus praesylvius which caused slowing or arrest in inspiration. Stimulation of an area in the most lateral part of the anterior sigmoid gyrus caused an increase in frequency of the respiratory movements. Munk (1882)

and Gianelli (1900) in the dog located areas in different parts of the cortex which produced an inhibitory response like that described by Bechterew and which they believed controlled the activity of either the inspiratory or the expiratory muscles.

Spencer (1894) in the cat and dog obtained slowing or arrest of respiration from an area including the caudal and lateral part of the olfactory tract and a small area of the laterally adjacent cortex. Increase in the rate of breathing was obtained in lightly anesthetized cats and dogs over a wide extent of the cerebral surface, but under deeper anesthesia this effect was most marked when the stimulus was applied to the cortex around the medial end of the sulcus praesylvius. Mavrakis and Dontas (1905) confirmed this latter finding on the dog. Bucy and Case (1936), in the dog, obtained slowing or arrest from an area adjacent and lateral to the rostral end of the coronal sulcus and an increase in rate from the lateral part of the anterior sigmoid gyrus.

Alterations in respiration from stimulation of the cerebral cortex in monkeys have been reported by Munk (1882), Spencer (1894), Bechterew (1911) and C. and O. Vogt (1919). Munk (1882) obtained arrest of respiration with the respiratory muscles in tetanic contraction from stimulation of the cortex just rostral to the curve of the inferior precentral sulcus and just medial to its medial end. Spencer (1894) reported arrest or slowing from stimulation of a large part of the orbital surface of the frontal lobe, the area from which the response was most easily obtained being just anterior to the junction of the lateral olfactory striae with the gyrus hippocampus. Bechterew (1911) obtained arrest of respiration in inspiration upon stimulation of an area a little anterior to the medial end of the sulcus precentralis inferior and an increase in rate from the cortex a little lateral to this area. C. and O. Vogt (1919) observed arrest or slowing from stimulation of the cortex just behind the lateral end of the sulcus precentralis inferior.

An analysis of the results of these investigators shows that they are far removed from unanimity not only as regards the position and extent of the cortical respiratory areas but also as regards the character of the elicitable response. In my investigations on the cat, dog, and monkey (*Macaca mulatta*) definite regions of the cortex were found which, when electrically stimulated, evoked specific alterations of the respiratory movements. Certain regions were found to have a predominantly inhibitory effect; others a predominantly excitatory effect. The inhibitory response was characterized usually by a slowing or complete arrest of breathing, and occasionally by a marked decrease in the amplitude of the respiratory excursions. The excitatory effect, on the other hand, was characterized by a marked increase in the rate of breathing. Although the responses obtained at different times varied in details, they did not depart from these fundamental characteristics.

II. Experimental Procedure

The usual technique for cortical stimulation was employed, the animal being kept under light ether anesthesia and stimulation of the cortex performed with 60 cycle alternating current using bipolar platinum electrodes 0.7 mm. in diameter and approximately 2 mm. apart. The electrodes were usually applied by hand, but in some instances they were carried by means of a suitable holder attached to a modified Horsley-Clarke stereotaxic instrument. The application of the electrodes by this method was found to possess certain obvious advantages not attainable by hand exploration, since they can be applied without undue pressure on the cortex, and being attached to the head of the animal, move with the head, thus avoiding risk of injury to the cortical surface. The anesthetic was administered from a Woulff bottle connected to a

rubber tube introduced through the mouth and larynx into the trachea. An uninterrupted passageway for air was thereby ensured and alterations of breathing from closure of the larynx were thus obviated.

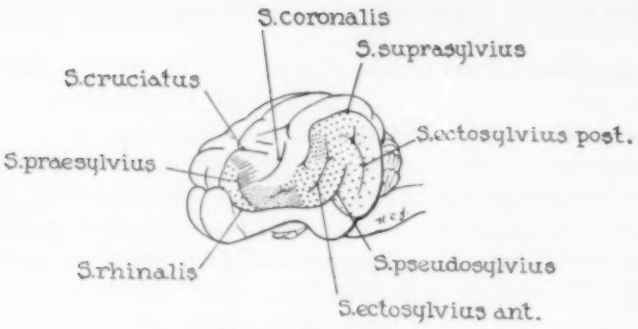
A closed system for recording the respiratory movements was used, because an open method like the one commonly employed was not found to give an accurate record, since its action depends upon intratracheal pressure changes rather than increase or decrease in the size of the thorax during the respiratory act. Accordingly, for the purpose of obtaining a kymographic record the tambour was connected to two rubber sphygmomanometer bags held in contact with the thorax and abdomen by an inelastic canvas belt, and inflated to the necessary degree. By this method inspiration compresses the bags and produces the upstroke on the record, expiration permits the compressed bags to relax and produces the downstroke. If desired, abdominal and thoracic respiration can be recorded separately. The whole system is sufficiently free of inertia to follow rapidly whatever changes in breathing occur. The arterial pressure was recorded from the femoral artery simultaneously with the respiration. The time in seconds and the duration of the stimulation were recorded by appropriate methods.

The extent of the responsive cortex was plotted on a tracing or drawing of the cortical surface and at the conclusion of the experiment the brain was fixed in 20 per cent formalin, after which blocks were taken, embedded in paraffin, serially sectioned at 20 microns and stained with thionin for cytoarchitectural study.

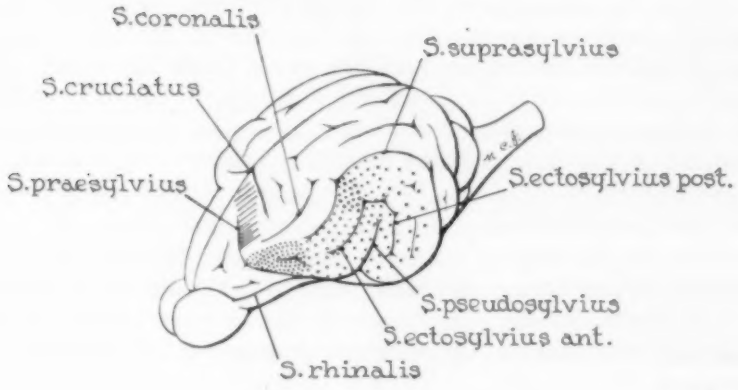
III. Results

Inhibition

In the cat and dog (Plate 1, Figs. 1 and 2) an inhibitory response was obtained from a relatively large area of the cerebral cortex when the animal was under very light ether anesthesia, the position of the inhibitory cortex being similar in the two species except as regards the cortex of the gyrus proreus. In the cat this gyrus usually gave an inhibitory response, but in the dog no respiratory effect was produced by its excitation. Increase in the depth of anesthesia resulted in decrease in size of the excitable field and finally in abolition of the response, an area in the anterior composite gyrus just caudal to the sulcus praesylvius being the last to succumb. This area is also the one from which an inhibitory response was most easily elicited, it having the lowest threshold of excitability, and it was from this area that arrest of breathing was most easily obtained. A stimulus of just sufficient strength to produce arrest here caused only a decrease in rate when applied to the more caudally situated part of the inhibitory field, and in general the effect became progressively less marked as the caudal edge of the field was approached. The one exception to this is furnished by a small area in the caudal part of the anterior ectosylvian gyrus (Plate 1, Figs. 1 and 2) for this area appears to have a lower threshold than the adjacent inhibitory field and produces a greater inhibitory effect when stimulated. However, it was never found to be such a powerful inhibitor as the area in the anterior composite gyrus.



1 CAT



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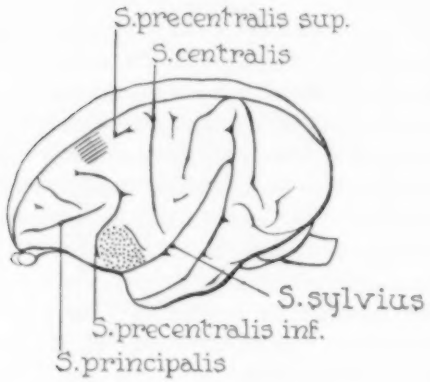

3 MONKEY

⁙ – Inhibitory cortex
▤ – Acceleratory cortex

PLATE 1

Areas of the cerebral cortex from which alterations of respiratory movements were elicited by electrical stimulation. The closest stippling and the closest lines indicate the areas from which the responses were most easily obtained.

Stimulation of the inhibitory area in the anterior composite gyrus of both cat and dog with current of a strength from 0.2 to 2 milliamperes, depending upon the degree of anesthesia, evoked an apparently immediate inhibitory response characterized by the thorax assuming the expiratory positions and maintaining this throughout the period of stimulation, provided the duration of the stimulation was not too prolonged (Plate II, Figs. 1 and 2). Upon cessation of the stimulus breathing was again resumed, often for a few seconds at a higher inspiratory and expiratory level than that which existed previously or there was an immediate return to normal without such a transition. This complete cessation of respiration could not be prolonged indefinitely, for after several seconds breathing begins again, although at a much slower rate than that existing prior to the application of the stimulus. An inspiration of great depth frequently initiated respiratory movements after the arrest. Deviations from this response were found to occur; for example, upon application of the stimulus the thorax sometimes assumed the expiratory position and then immediately, or after the lapse of one or several seconds of complete cessation, a slow inspiration took place over a period of several seconds, reaching a degree equal to or greater than that existing previously, after which breathing again began but at a much slower rate than before. Upon cessation of the stimulus breathing returned to the previous rate and amplitude. If a weaker current was used, or if the excitability of the cortex decreased, then a slowing of respiration occurred either with or without a change in amplitude and the response became less marked as the duration of the stimulation increased.

Application of the stimulating current at various portions of the inspiratory phase usually resulted in the termination of the process of inspiration, the thorax quickly assuming the expiratory position, after which any of the responses previously described might occur. At times, however, breathing was arrested and the thorax remained in the position it occupied when the stimulus was applied, and after cessation of the stimulus the phase which had been interrupted was completed. On the other hand, breathing may be arrested for a varying length of time, after which a slow inspiration lasting over several seconds may occur until the thorax is expanded to the same or to a greater extent than it was prior to the stimulation. If the stimulation is continued respirations are resumed at a much slower rate than that existing before the stimulus was applied or if the current is discontinued breathing rapidly returns to normal.

A less pronounced inhibitory effect was obtained from most of the cortex of the sylvian and ectosylvian gyri. Stimulation of this region with a current of moderate strength usually resulted in a slowing of respiration without much change in amplitude.

Stimulation of the cortex of the gyrus proreus on both the lateral and mesial surfaces of the hemisphere in the cat usually resulted in a pronounced decrease in the respiratory rate. Arrest of respiration was rarely obtained and the inhibitory response was elicitable only when the anesthesia was extremely light. Strangely enough no effect upon respiration was ever obtained from

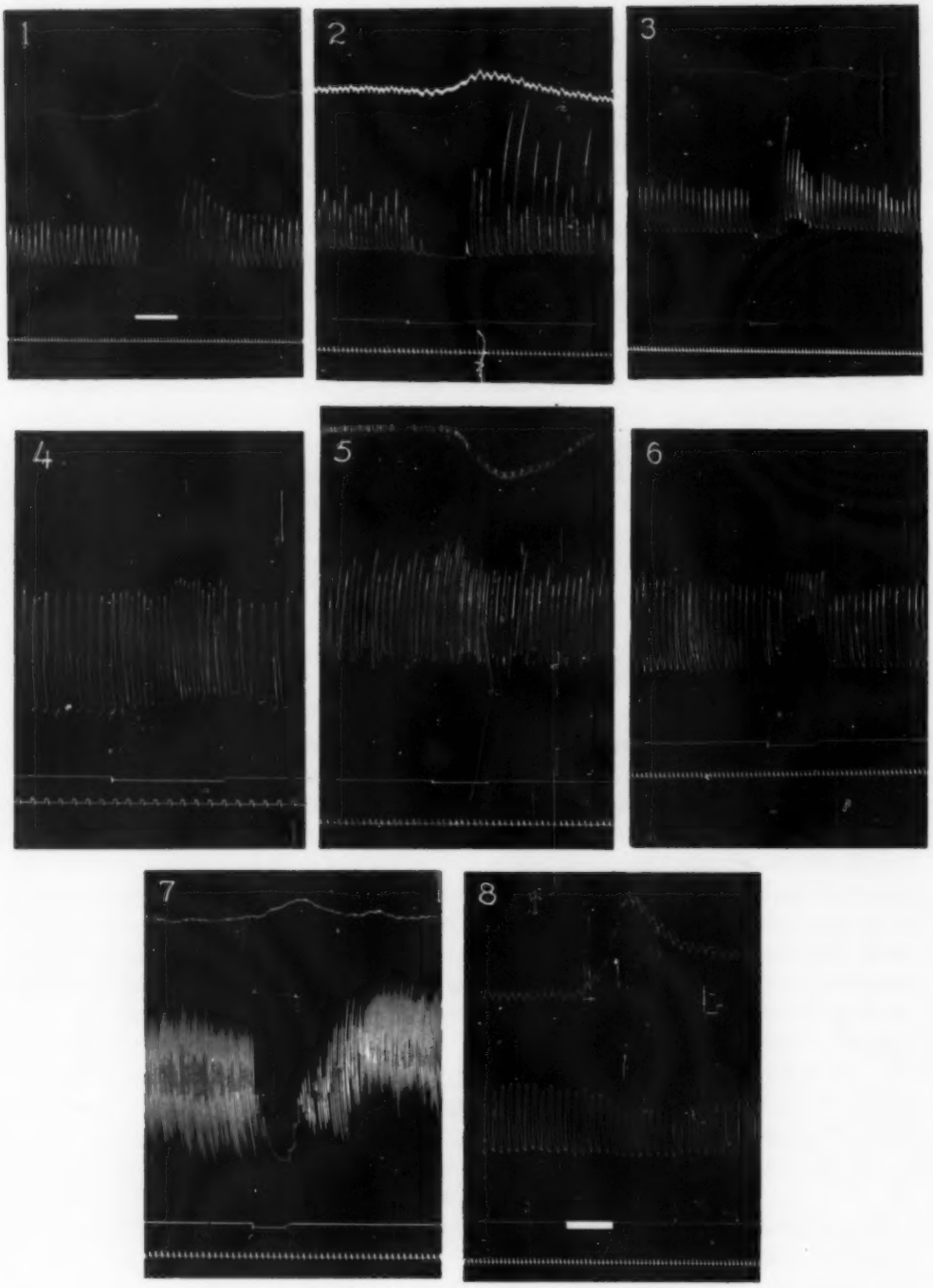

PLATE 2

FIGS. 1, 2, and 3. Inhibition of respiration from electrical stimulation of the inhibitory cortex of the cat, dog, and monkey, respectively.

FIGS. 4, 5, and 6. Acceleration of respiration from electrical stimulation of the acceleratory cortex of the cat, dog, and monkey, respectively.

FIG. 7. Arrest of panting from stimulation of the inhibitory area in the dog.

FIG. 8. The rise of arterial pressure elicited by stimulation of the inhibitory area in the anterior composite gyrus in a curarized cat under artificial respiration.

stimulation of this gyrus in the dog, even though stimuli of inordinate intensity were used.

The inhibitory area in the monkey (Plate 1, Fig. 3) is much more limited in extent than in either the dog or the cat and its boundary is more sharply defined. It is situated caudal to the lateral end of the inferior precentral sulcus and is limited laterally by the sylvian sulcus. Its caudal limit is frequently defined by a shallow sulcus occurring in the precentral gyrus at this point, but occasionally a decreased rate or a decreased amplitude was obtained upon stimulation just behind this sulcus. Stimulation of this area produced an inhibitory effect upon breathing similar to that obtained in the cat and the dog, i.e., arrest of breathing in which the thorax quickly assumed the expiratory position (Plate 2, Fig. 3). Resumption of breathing, subsequent to the arrest, is more frequently initiated by an extraordinarily deep inspiration in the monkey than in the cat or dog. Furthermore, if a weaker current was used or if the excitability of the cortex became lowered, stimulation usually produced a great decrease in amplitude without much change in rate, while in the cat and the dog slowing without much change in amplitude usually occurred.

The cortical respiratory inhibitory areas when stimulated not only exert their influence upon breathing of the usual type, but also have a pronounced inhibitory effect upon panting in both the cat and dog. The area in the anterior composite gyrus that is the most powerful inhibitor of normal breathing still retains its supremacy in the panting animal as evidenced by the fact that stimulation of this area with a current of moderate strength causes a cessation of panting (Plate 2, Fig. 7). In this instance as in the case of arrest of normal breathing, the thorax usually assumes the expiratory position. Stimulation with a weaker current slows but does not arrest panting and this is the result usually obtained from excitation of the remainder of the inhibitory field, only a slight effect being produced from stimulation of its caudal part.

The increase in rate and amplitude of breathing that is seen upon stimulation of a sensory nerve, e.g., the sciatic, can be abolished or diminished by stimulation of the inhibitory area, the inhibitory effect being most pronounced when the area in the anterior composite gyrus is stimulated and when the sciatic stimulus is at or just above threshold. At this level the respiratory effect of sensory stimulation is completely abolished. If a stronger stimulus is applied to the nerve the effect is diminished by cortical stimulation, and in general the stronger the sensory stimulus the less the cortical response.

Acceleration

The cortical region from which acceleration in the rate of breathing was obtained is situated in both the cat and dog in the anterior sigmoid gyrus and the immediately adjacent cortex of the medial surface of the hemisphere, the response being most easily elicited from the rostrolateral part of the gyrus (Plate 1, Figs. 1 and 2). In the cat under very light anesthesia an acceleratory effect, characterized by a very active expiration, was also obtained from a small area situated just at the rostral end of the sulcus ectosylvius anterior

between the sulcus diagonalis above and the sulcus rhinalis below. A remarkable characteristic of this area is that a complete reversal of response was obtained when the animal was under deeper anesthesia, stimulation then producing an inhibitory effect.

In comparison to the extent of the inhibitory area the acceleratory area in both cat and dog is relatively small, but it is not so disproportionately small as appears in the drawing for it extends into the depths of the sulcus praesylvius forming its caudal wall.

The acceleratory response in the monkey was most easily elicited from the cortex just rostral to the superior precentral sulcus and from a small area of the immediately adjacent cortex of the medial surface of the hemisphere (Plate 1, Fig. 3).

In the cat, dog, and monkey the acceleratory areas usually respond with an increase in the rate of respiration that may amount to several times the normal (Plate 2, Figs. 4, 5 and 6). This increased rate is characterized by a decrease in the duration of the expiratory pause and may occur with or without a change in the amplitude of the respiratory excursions. In an apparently normally excitable cortex the degree of acceleration appears to depend to a certain extent upon the intensity of the stimulus. A limit, however, is reached beyond which no further increase in rate is obtainable. Acceleration in the monkey was never obtained to the same degree as in the cat and the dog. In the latter animals, under very light anesthesia, typical panting respirations were sometimes produced.

In all animals both the inhibitory and acceleratory areas are present in corresponding positions on both sides of the brain and bilateral stimulation is more effective than unilateral. Isolation of the inhibitory cortex of the anterior composite gyrus or the acceleratory cortex of the rostral part of the anterior sigmoid gyrus by an incision through all the cortical layers does not abolish the response, but undercutting these areas without isolation renders them unresponsive. The response, however, can be obtained by stimulation of the cut ends of the underlying fibers, subsequent to removal of the cortical areas.

The responses were elicitable after bilateral section of the phrenic nerves and the vago-sympathetic trunks. They were also obtained after section of the spinal cord below the origin of the phrenics, thus demonstrating that the inhibitory effect is mediated over both intercostal and phrenic nerves and in the absence of one set the other suffices. Section of the corpus callosum does not abolish the responsiveness of the areas in either hemisphere, and removal of one hemisphere does not seem to affect the responsiveness of the acceleratory and inhibitory cortex in the other.

Reversal of response was found to occur from two cortical regions in the cat. The gyrus proreus which usually produced a marked inhibition of breathing occasionally responded with acceleration and a small cortical area near the rostral end of the sulcus ectosylvius anterior responded with acceleration under very light anesthesia and with inhibition when the anesthesia was

deeper. From the remainder of the respiratory fields a reversal of response has not been encountered.

IV. Other Responses Occurring Simultaneously with the Respiratory Alterations

In cortical stimulation experiments a single effect is not always obtained from stimulation of one area, and even those areas which appear to give a single discrete response probably are concerned with functions other than those indicated by the observable one. It is not surprising therefore in the face of the indicated plurality of functions in the cerebral cortex, that other responses are elicited simultaneously with those pertaining to respiration.

In the very lightly anesthetized cat stimulation of the gyrus proreus not only effects an inhibitory response upon breathing but provokes a striking effect upon certain somatic responses. Body and extremity movements spontaneously executed are immediately stopped, rigidly extended extremities relax, lashing of the tail disappears, and the hyperactive animal appears to become thoroughly inactive and calm, at least in so far as ordinarily observable activity is concerned. In this instance inhibition of breathing seems to be part of a generalized inhibitory effect produced by excitation of this part of the cortex. In the dog, however, similar inhibitory responses were not produced by stimulation of this gyrus. The generalized inhibition that occurs in the cat upon stimulation of the gyrus proreus, is also evident upon stimulation of most of the remainder of the respiratory inhibitory area.

In both the cat and dog, there may occur, simultaneously with the respiratory arrest, mastication, licking or swallowing movements, either singly or in combination, as a result of stimulation of the most excitable part of the inhibitory area in the gyrus compositus anterior; similar results are obtained as a result of excitation of the inhibitory area in the monkey. These accompanying effects are not obtained as a result of excitation of the more caudal part of the respiratory inhibitory field in the cat and dog. This latter observation combined with the fact that respiratory arrest or slowing can be obtained without the swallowing, chewing or licking movements, seems to exclude these processes as a cause of the inhibition of breathing produced by cortical stimulation.

Another frequent manifestation concomitant with the respiratory inhibition is that characterized by a marked rise in the arterial pressure with or without a decrease in the cardiac rate and an increase in the pulse pressure (Plate 2, Fig. 1). As regards this particular study the rise in arterial pressure must be seriously considered because it stimulates the carotid sinus and thus may produce respiratory changes reflexly (Heymans and Bouckaert, 1933). Although it is inconceivable that an increase in arterial pressure of the degree obtained in these experiments would suffice to arrest breathing, it is possible that such an increase might effect a reflex decrease in the rate of breathing. That the rise in arterial pressure is effected by a nervous mechanism independent of that producing respiratory inhibition is attested by the finding that the

arterial pressure increase does not always accompany the respiratory response and when it does occur increase in the depth of anesthesia abolishes the cardiovascular response but leaves intact the respiratory one. The crucial experiment, however, consisted in stimulation of the respiratory inhibitory area in the gyrus compositus after removal of both carotid sinuses and both carotid bodies. Under such conditions when carotid sinus effects are definitely excluded respiratory inhibition still occurred. The independence of the two processes is further established by the fact that the increase in arterial pressure is obtained from the inhibitory area in the gyrus compositus anterior when the animal is under artificial respiration after the respiratory movements have been paralyzed by curare (Plate 2, Fig. 8).

From the acceleratory area a marked fall in arterial pressure usually occurs simultaneously with the respiratory acceleration (Plate 2, Fig. 5). As is the case with inhibition the acceleratory effect is sometimes obtained without a change in the arterial pressure. In all three species the acceleratory phenomenon was usually accompanied by turning of the head and eyes toward the contralateral side, by bilateral dilatation of the pupils and by movement of the contralateral foreleg.

V. Cytoarchitecture

The cytoarchitecture of the cortical region from which respiratory alterations were obtained is of interest from the point of view of the relation between structure and function, for in cat, dog and monkey, the acceleratory cortex is situated predominantly in the area frontalis agranularis (area 6 of Brodmann), more especially in the part of this area designated by C. and O. Vogt (1919) for the monkey as area 6a. In all three animals this cortex is characterized by an indistinct lamination, by a paucity of granular cells and by the absence of definite granular layers. In the cat and dog this area is relatively small as compared to the same area in the monkey and not so well differentiated. It is therefore not surprising to find that the acceleratory area in the cat and dog extends caudally into the transition zone between areas 4 and 6a and rostrally into the transition zone between area 6a and the poorly differentiated cortex of the gyrus proreus. This more or less gradual structural change between area 6a and the cortex of the gyrus proreus belies the abrupt physiological change which is evident upon electrical excitation, for the small vein that usually is found leaving the medial end of the sulcus praesylvius to enter the superior longitudinal sinus by passing across the junction of the gyrus proreus and the gyrus sigmoideus anterior often marks the rostral boundary of the acceleratory cortex. In many cats stimulation just caudal to this vein produced acceleration while stimulation just rostral to it produced inhibition. In a similar manner in both cat and dog a small vein passing from the rostral end of the coronal sulcus to the sulcus praesylvius often marked an abrupt change from acceleratory to inhibitory cortex. Thus far it has not been possible to correlate these sudden physiological changes with any abrupt cytoarchitectural transitions.

The inhibitory cortex in the cat and dog occupies a relatively large part of the cortical surface. In view of this it is not surprising to find that the region from which inhibition is obtained consists of several cytoarchitecturally different areas. However, the cortical area in the cat and dog from which inhibition is most easily elicited (that is, the area in the anterior composite gyrus) and the inhibitory area in the monkey consist of cortex similar to that described for the acceleratory area, but are cytoarchitecturally differentiated from it chiefly by the presence of a greater number of granular cells and by the indication of granular layers. This inhibitory area therefore belongs to the lateral part of area 6 and has been designated by C. and O. Vogt (1919) for the monkey as area 6b, the area frontalis dysgranularis. In the cat and dog the less powerful inhibitory cortex caudal to this area is distinctly granular in type, having definite granular layers.

The gyrus proreus from which an inhibitory response is usually obtained in the cat possesses, in its caudal part, cortex similar to that of area 6a, but this undergoes a gradual transition so that more rostrally this gyrus has what appears to be a rather undifferentiated type of cortex which Langworthy (1928) describes as having an embryonic appearance. In the dog no alterations of breathing were obtained from cortex of this type.

VI. Comment

The evidence obtained in this investigation indicates that the premotor area (area 6) is primarily the one from which both acceleration and inhibition can be obtained by electrical stimulation. The fact that acceleration was usually obtained from excitation of the medial part of this area and inhibition from excitation of its lateral part lends further physiological evidence in support of the already made cytoarchitectural separation of area 6 into a medial part (area 6a) and a lateral part (area 6b). In no instance were respiratory alterations obtained from excitation of cortex which could be unmistakably identified as motor cortex (area 4). This finding therefore refutes the contention of Bochefontaine (1876) and François-Franck (1887) that alterations of breathing could only be elicited by stimulation of the sigmoid gyri in the cat and dog and that no relation exists between the point stimulated and the response elicited. Furthermore, the finding that the inhibitory cortex of the anterior composite gyrus in both cat and dog appears to belong cytoarchitecturally to area 6 is not in agreement with Brodmann's (1906) concept of the structure of this region, for in the cat he designated it as part of the agranular gigantopyramidal area (area 4). Also, in the dog the inhibitory cortex of the anterior composite gyrus was found to possess a structure which marks it as belonging to area 6b and not to area 4 as Klempin (1921) reported. The fact that the acceleratory cortex belongs to the frontal adversive field and that the inhibitory cortex of the anterior composite gyrus belongs to the area from which mastication and deglutition is elicited is also evidence against either area being homologous with area 4 of primates.

In the monkey (*Macaca mulatta*) the acceleratory area is situated in cor-

tex typical of area 6a and the inhibitory area in cortex typical of area 6b. C. and O. Vogt (1919) in *Cercopithecus* limited the respiratory inhibitory field chiefly to their area 6bβ, but the results of my investigations do not indicate such a fine distinction because all of area 6b was found to have an inhibitory effect.

Even though the gyrus proreus in both the cat and dog consists for the most part of undifferentiated cortex of a structurally similar type, the inhibitory effect elicited by stimulation of this gyrus in the cat was not found to occur in the dog even when strong stimuli were used. However, Polimanti (1906) reported inhibition of respiration from stimulation of this gyrus in the dog. Not only has this finding of Polimanti (1906) not been confirmed by this investigation but in addition, no evidence has been obtained to support the contention of Gianelli (1900) and others that separate cortical areas exist for the innervation of the inspiratory and expiratory muscles respectively.

That the cortex normally exerts an influence on panting in the cat and dog is suggested by the finding that respirations simulating panting can be produced by stimulation of the acceleratory area, and also by the fact that panting can be inhibited to the point of cessation by stimulation of the inhibitory area. Furthermore, Pinkston, Bard and Rioch (1934) found that after removal of the cerebral cortex in cats and dogs true polypneic panting was absent and in its stead a long delayed slow hyperpnea occurred under conditions which would have promptly produced panting of the usual type.

The course of the corticofugal impulses effecting respiratory alterations is not known, but the fact that such impulses are able to exert their influence through extrapyramidal pathways seems evident from the investigations of Tower (1936) who obtained alterations of breathing from cortical stimulation in the cat after section of both corticospinal tracts at the upper level of the pons. It is likely that the impulses set up by stimulation of the areas in either hemisphere exert their influence primarily upon the myelencephalic respiratory mechanism rather than directly upon the spinal motoneurones since the respiratory muscles appear to be affected bilaterally as a functional unit.

The cortical effect presumably may either increase the rate of discharge of the volleys of impulses from the myelencephalic "respiratory center" thus producing acceleration of breathing, or it may entirely prevent the discharge thus causing cessation, or it may increase or decrease the frequency of the impulses composing each volley thus producing either a respiration of greater or lesser amplitude, or the combinations of the above may occur so as to produce slowing or acceleration with increased or decreased amplitude.

Summary

Alterations in breathing characterized by either inhibition or acceleration were produced by electrical stimulation of certain regions of the cerebral cortex in the cat, dog, and monkey (*Macaca mulatta*). In the cat and dog, under light ether anesthesia, an inhibitory effect upon breathing characterized by a temporary cessation or slowing was most easily elicited from an area in

the gyrus compositus anterior. A less marked but definite inhibitory effect was obtained from most of the cortex of the sylvian and ectosylvian gyri, and in the cat from the gyrus proreus as well. Increase in the depth of anesthesia resulted in abolition of the response, the area in the anterior composite gyrus being the last to succumb. Stimulation of the inhibitory area not only slowed or arrested panting, but also abolished or prevented the alterations in breathing that are ordinarily produced by sensory stimulation.

The inhibitory area in the monkey is situated in the cortical field just caudal to the lower end of the sulcus precentralis inferior.

The acceleratory response was most easily elicited in the cat and dog from the rostro-lateral part of the anterior sigmoid gyrus and the adjacent cortex forming the caudal wall of the sulcus praesylvius, and in the monkey from stimulation of an area just rostral to the sulcus precentralis superior. In the cat and dog the acceleration at times was so great as to simulate panting, but in the monkey an increase in rate of such magnitude was never obtained.

Various types of somatic and autonomic responses were obtained simultaneously with the respiratory changes, but these have been excluded as possible causes of the respiratory alterations.

The region from which the acceleratory response was most easily elicited belongs cytoarchitecturally to area 6a in all three animals; that from which the inhibitory response was most easily obtained belongs to area 6b.

The presence in the cat, dog, and monkey of cortical areas possessing similar cytoarchitectural structure and yielding similar physiological responses, suggests the existence of a fundamental plan for the cortical control of respiration in the general scheme of cerebral cortical evolution.

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FUNCTIONAL ORGANIZATION IN THE SENSORY CORTEX OF THE MONKEY (*MACACA MULATTA*)*

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INTRODUCTION

IN 1924[5,6] the location and extent of the sensory cortex were established in the brain of the monkey (*Macaca*) by means of the method of local strychninization. This cortex was found to occupy a large portion of the post- and precentral region, and to comprise three major subdivisions (the leg-, arm- and face-subdivisions). This mapping was achieved by the local application of minute quantities of strychnine to very small portions of the cortex; such applications, if performed within the sensory cortex, resulting in marked symptoms of sensory excitation (paraesthesiae, hyperaesthesia and hyperalgesia) in different parts of the body.

Such an application of strychnine not only produces symptoms of hypersensitivity but also typical changes in the electrocorticogram (ECG.),† namely the appearance of large, rapid potential fluctuations—"strychnine-spikes." The occurrence of such spikes is not limited to the sensory cortex; they appear upon local strychninization of any portion of the cerebral cortex. The distribution of the spikes, however, is dissimilar when the areas are dissimilar.

It is first of all with these dissimilarities in distribution that the present paper deals, both in regard to the distribution of the spikes within the cytoarchitectonic area, of which a part has been strychninized, and in regard to the distribution of the spikes in architectonic areas other than the area locally strychninized. Furthermore this paper deals with the observation that strychninization of two definite areas results, besides producing strychnine-spikes in other areas, in a temporary suppression of the electrical activity of another area. Finally the results obtained with strychninization were corroborated in experiments with electrical stimulation of various areas and recording of the electrical after-discharge in other areas.

METHODS

The experiments were all performed on monkeys (*Macaca mulatta*), either fully anesthetized with Dial‡ (0.45 cc. per kilogram, half of the dose given intraperitoneally, half intramuscularly), or ether, or operated upon under

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* The expenses of this investigation were defrayed by a grant from the Fluid Research Funds of the Yale University School of Medicine.

† Although realizing the hybrid origin of this word, we wish to use the term to designate conveniently the record of the electrical activity of the cortex taken directly from its exposed surface and to differentiate this record from the electroencephalogram (Berger), in which the electrical activity of the cortex is recorded indirectly, through the skull of the subject, or at least not directly from the cortex.

‡ We wish to thank the Ciba Company for kindly putting the Dial at our disposal.

Vinylether* and curarized, but studied while awake. The strychnine (3 per cent solution, colored with toluidine blue) was always applied to a very small portion of the cortex, measuring only 1–4 square mm., either by touching the cortex at the desired locus with a pledget of cotton wool twisted around the ends of an irisforceps and moistened with the strychnine solution or by covering the cortex with a very small piece of filter paper, soaked with the strychnine solution. Before application of the pledget or filter paper the excess strychnine solution was carefully removed from it. For brevity we will refer to the application of strychnine to a few square millimeters of cortex, by either procedure, as "local strychninization."

The electrocorticograms were taken from various portions of the cortex with two fine Ag-AgCl electrodes, 3 to 4 mm. apart, this being the optimal distance for recording the ECG. with this type of electrodes. In most of the experiments the electrical activity was recorded with a cathode ray oscillograph after suitable amplification through a two-stage DC-amplifier. This method permits only successive electrocorticograms. Later AC-amplification with a four-element Westinghouse oscillograph was used for simultaneous recording of four electrocorticograms. The results of these experiments confirmed the previous observations. In many experiments bipolar electrical stimulation of one cortical focus was performed and the changes in the electrocorticograms (electrical after-discharge) of various foci examined.

Results

In Figure 1 is shown the location and extent of the sensory cortex of the brain of *Macaca mulatta*, with the subdivision into its leg- arm-, and face-areas.[5]

It should be pointed out that, apart from the incorporation of the cytoarchitectonic denominations, the present diagram differs in two respects from that of 1924, namely in the relation of the beginning and end of the sulcus interparietalis to the various subdivisions. The diagram of 1924 was based upon the study of 20 monkeys, in which only a few experiments could be devoted to the areas in question. The present diagram is based upon a large number of experiments and represents more truly an "average" of the findings in relation to the configuration of the surface of the macaca's brain, which differs so much from animal to animal.

Within each subdivision are also represented some of its cytoarchitectonic areas, simplified and modified after the investigations of Brodmann[1,2] and C. and O. Vogt.[9] The main deviation from their diagrams is the inclusion in Figure 1 of a field 4-s between 4 and 6a. From our diagram it can be readily understood what is meant in this paper by local strychninization within arm 4 area (A.4), leg 6a area (L.6a), or face 2 area (F.2), etc.

1. Changes of the ECG. in general following local strychninization.

Local strychninization of any portion of the cerebral cortex elicits typical changes in the ECG. at the site of strychninization, namely the appearance of "strychnine-spikes." The first alteration, within a few seconds after the application of the strychnine, is an augmentation of the general electrical

* The Vinylether (Vinethene) was kindly put at our disposal by the Merck Company.

activity of the cortex; 30 to 60 secs. later the strychnine-spikes begin to appear which are fully developed in about 2 to 3 minutes. With the development of the spikes the "background"-activity, i.e. the potential fluctuations between the spikes, often markedly diminishes. At the end of about 15 minutes, the spikes begin to decrease slowly in size and frequency, while the background-activity is returning to its original magnitude. In 20 to 40 minutes the ECG. has usually regained its original characteristics. Renewed local application of strychnine then reinduces the whole train of events.

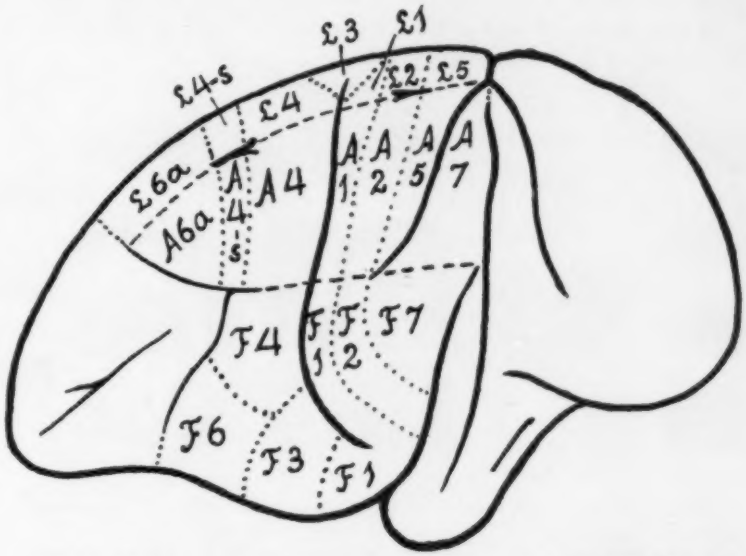


FIG. 1. Extent and location of the sensory cortex in the brain of *Macaca mulatta*, with some of the architectonic areas, appearing on the surface of the brain (slightly modified after Brodmann and C. and O. Vogt). The essential deviation from their diagrams is the introduction of an area L.4-s and A.4-s.

The configuration of the strychnine-spikes, recorded from the surface of the hemisphere, depends upon a number of factors, of which the most important are the size and positions of the electrodes and the stage of strychninization. We cannot enter here into a discussion of these relations; they have been dealt with to some extent at the Atlantic City meeting of the American Neurological Association, June, 1937 (See Transactions of that meeting).

Local strychninization anywhere within the *sensory* cortex (see Figure 1) produces spikes not only in the ECG. of the minute area strychninized, but also in other portions of the sensory cortex. The distribution of these spikes is wide-spread, but not fortuitous. It is constant for any given area, but different for the various cytoarchitectonic areas and the various major subdivisions of the sensory cortex. This distribution is altered neither by deep undercutting of the whole sensory cortex, nor by thermocoagulation of a narrow circular strip of cortex, throughout its entire thickness, around the area strychninized.

2. Distribution of the strychnine-spikes within the area locally strychninized.

The distribution of the spikes within an area locally strychninized differs for various regions of the cerebral cortex. This distribution is very restricted within the visual cortex (area 17 of Brodmann) and within area 5 of the sensory cortex: large spikes are present at the site of strychninization, small spikes in its immediate vicinity. One or two millimeters and farther away from the strychninized locus spikes are absent (see Figure 2).

In other portions of the cerebral cortex the distribution of the strychnine-spikes is much wider. Local strychninization of A.4 for instance results in a "firing" of the whole of this area, i.e., results in the appearance of spikes in the ECG. of all of A.4 (see Figure 3).

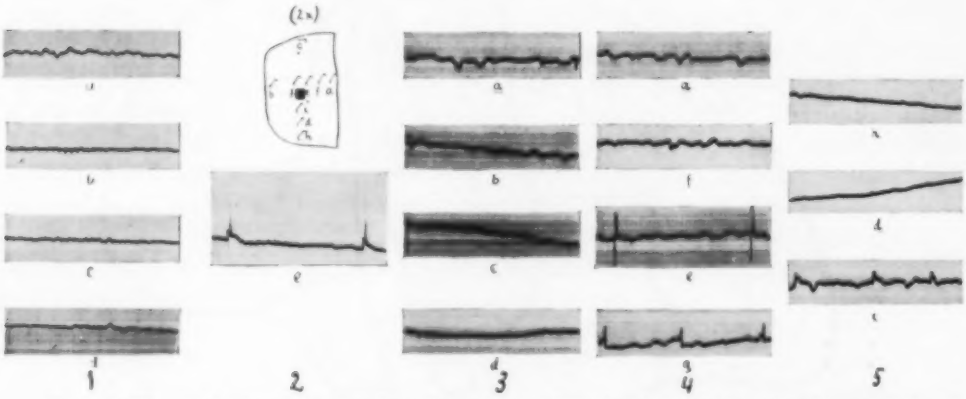


FIG. 2. Figure 2 gives the results of local strychninization of the visual cortex (area 17 of Brodmann) and shows that the strychnine-spikes appear only in the immediate vicinity of the strychninized area. First column shows the ECGs before the strychninization. The other ECGs of the loci indicated by the letterings at different times after the strychninization. Same amplification throughout. Column 1 before, the other columns *after* the strychninization. ECG. of column 2 (e) taken 2 minutes after, those of column 3, 4 minutes; column 4, 7 minutes and column 5, 10 minutes after the strychninization.

3. Distribution of the strychnine-spikes in other areas than the one strychninized.

One finds the widest distribution of the strychnine-spikes in the *sensory* cortex. The local strychninization of any cytoarchitectonic area within this cortex produces spikes in several other constituent areas. It is advisable to take up the various subdivisions of the sensory cortex separately. We shall first describe the findings relating to the arm-subdivision. Here the following results obtain: local strychninization of area 7 "fires" not only this area itself, but also areas 5, 2, 1 and 4; that of area 5 "fires" areas 2, 1 and 4; that of area 2 "fires" also areas 7, 5 and 4; that of area 1 "fires" also areas 7, 5 and 2; that of area 4 "fires" also areas 7, 5, 2 and 1.

In the case of the leg-subdivision the same results are found so far as the homologous areas, mentioned for the arm-subdivision, are concerned. In the leg-subdivision a portion of area 3 appears on the surface of the hemisphere, so that there this area can be locally strychninized on its surface. Such

strychninization results in a "firing" of areas L.5, L.2, L.1, L.3 itself, and L.4. In the face-subdivision it was found that local strychninization of its postcentral region "fires" this region and also the precentral portion, and vice-versa. As yet we have not enough experimental data to make a more detailed statement for this subdivision.

What is common to all of these cases is: (1) that strychnine-spikes are always largest in the area strychninized locally, and diminish in size with increase of distance of the area "set on fire" from the area strychninized; (2) that the distribution of the spikes is limited to the subdivision locally strychninized; and finally (3) that area 6a is not "fired."

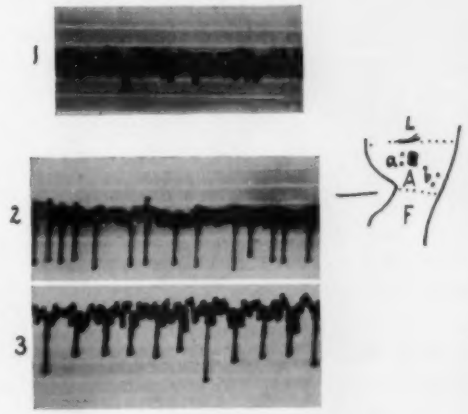


FIG. 3. Figure 3 shows that local strychninization of A.4 is followed by large spikes throughout this area. Record 1 is ECG. before strychnine-application. Record 2 gives the ECG. at *a*, record 3 the ECG. at *b* at the acme of the strychnine-spikes.

Figure 4 shows: (1) that local strychninization of A.5 does not "fire" this area, even in the vicinity of the locus strychninized; (2) that it "fires" A.4; (3) that it does not "fire" the precentral and postcentral region of the face- and leg-subdivisions. Figure 5 shows: (1) that local strychninization of L.4 "fires" L.4, L.2 and L.5; (2) that the spikes diminish in size the farther away the area "fired" is from L.4; (3) that the arm-subdivision is not "fired" and (4) that L.6a is not "fired."

In both Figures 4 and 5 the gradual return toward the normal ECG., present before the local strychninization, can be observed.

The sensory cortex situated in front of L.4 and A.4 requires separate mention. Here two areas, designated 6a and 4-s in Figure 1, can be differentiated.

First of all it should be stated that area 6a is the only portion of the sensory cortex which is not fired by the local strychninization of any other portion of the sensory cortex. Secondly, the local strychninization of either portion of

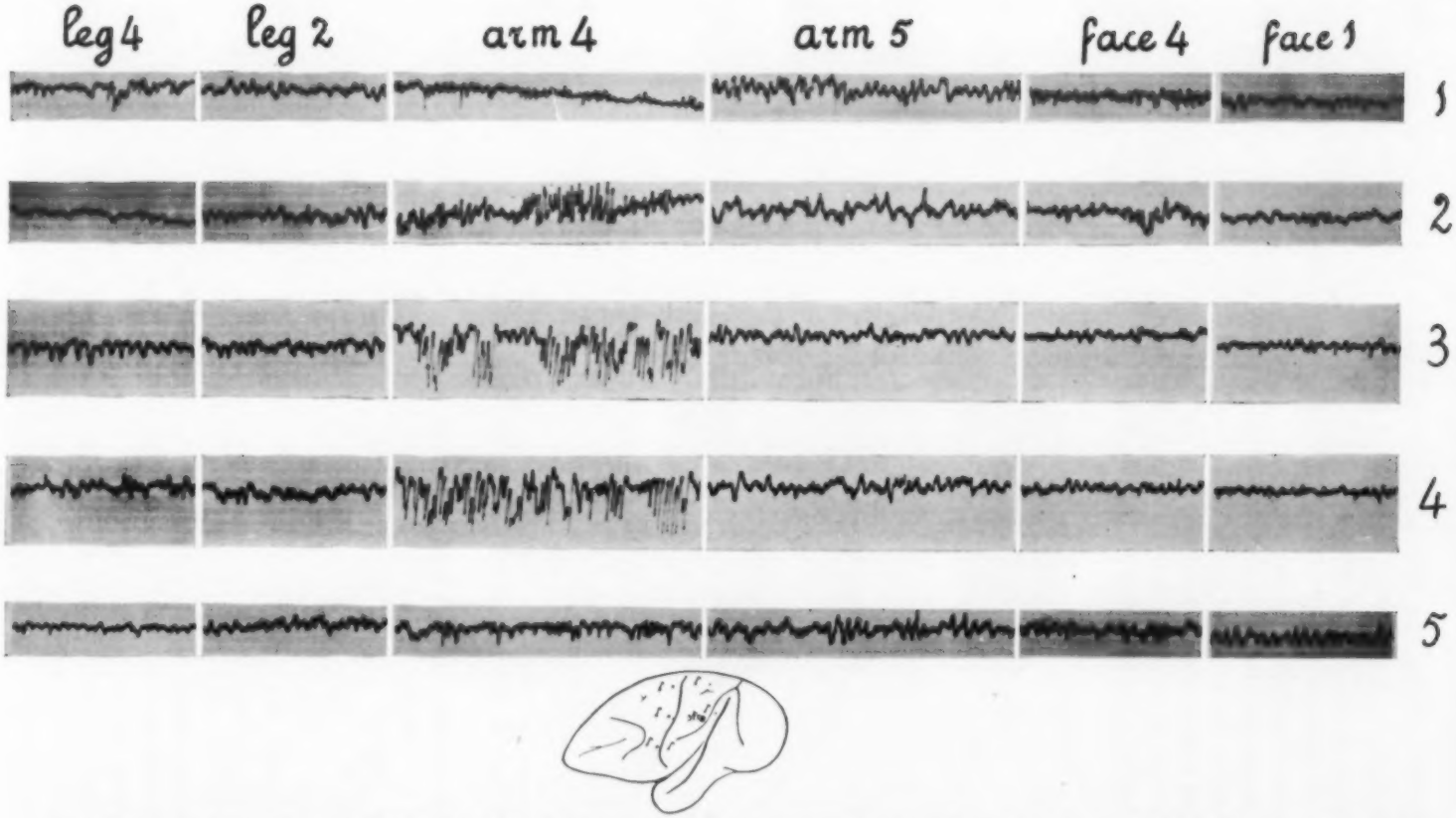


FIG. 4. Figure 4 (experiment of April 10, 1936; Dial-narcosis) shows the results of local strychninization of A.5. No apparent changes in the ECG. of A.5 immediately outside of the strychninized area. Enormous increase of the electrical activity in A.4. No changes in the ECG. of L.2, L.4, F.1 (and F.2) and F.4 (functional boundaries between the three major subdivisions). Row 1 gives the ECGs before the local strychninization of A.5, rows 2, 3, 4 and 5 at different times after this strychninization. Note the return to normal of the ECG. of A.4 in row 5.

area 6a, of L.6a *or* of A.6a "fires" all constituent areas of the leg- *and* of the arm-subdivisions, i.e. strychnine-spikes appear in L.6a, L.4, L.3, L.1, L.2, L.5, A.6a, A.4, A.1, A.2, A.5 and A.7.

The local strychninization of area 4-s produced equally striking results. Strychnine-spikes appeared in all of area 4-s, irrespective of the locus of strychninization in this area, i.e. in either A.4-s or L.4-s, and in the postcentral portions of the arm- *and* of the leg-subdivisions. The new observation in this set of experiments was that a temporary *suppression* of the electrical activity of area 4 ensued, both in L.4 and in A.4. See Figure 6. Within a few minutes after the application of the strychnine to either L.4-s or A.4-s the electrical activity of L.4 and A.4 diminished considerably, while strychnine-spikes were present in the electrocorticograms of all the postcentral areas of the leg- *and* of the arm-subdivisions. After about 15 minutes, when the strychnine-spikes in these areas began to diminish in size and frequency, the ECG. in area 4-s began to come back and 20 to 25 minutes after the application had returned to its normal magnitude, simultaneously with the disappearance of the strychnine-spikes in the other portions of the leg- and arm-subdivisions. No changes were apparent in the ECG. of area 6a. This result is shown in Figure 6.

Areas 6a and 4-s have, therefore, this in common that no functional boundary between the arm- and leg-subdivisions is apparent so far as the changes in the ECG. following local strychninization of these areas is concerned, both in regard to the distribution of the strychnine-spikes and in the case of area 4-s to the temporary suppression of the electrical activity of area 4.

The local strychninization of area 1, like that of area 4-s, suppresses temporarily the electrical activity of area 4, while "firing" the other postcentral areas of the sensory cortex; it does not produce any changes in the ECG. of area 6a. In the case of the local strychninization of area 1, however, these changes in the ECG. are restricted to the subdivision to which the minute strychninized portion of area 1 belongs. The results of the local strychninization of area 1 are shown in Figure 7.

4. Electrical stimulation of one locus producing electrical after-discharge in other loci of the sensory cortex.

From previous work[8] we knew that electrical stimulation of such a type (sufficiently long duration, long pulses, etc.) that when applied to the "motor" cortex motor after-discharge occurs, will at lower voltages still produce an electrical after-discharge, evidenced in the ECG., though no peripheral motor response is manifest. We have found that when any focus of the sensory cortex is thus stimulated the electrical after-discharge is present not only at the site of stimulation and its immediate vicinity, but also at other foci, in other areas of this cortex. Thus we have here a method to check the results obtained in the strychnine experiments.

It was found that the distribution of this after-discharge upon appropriate

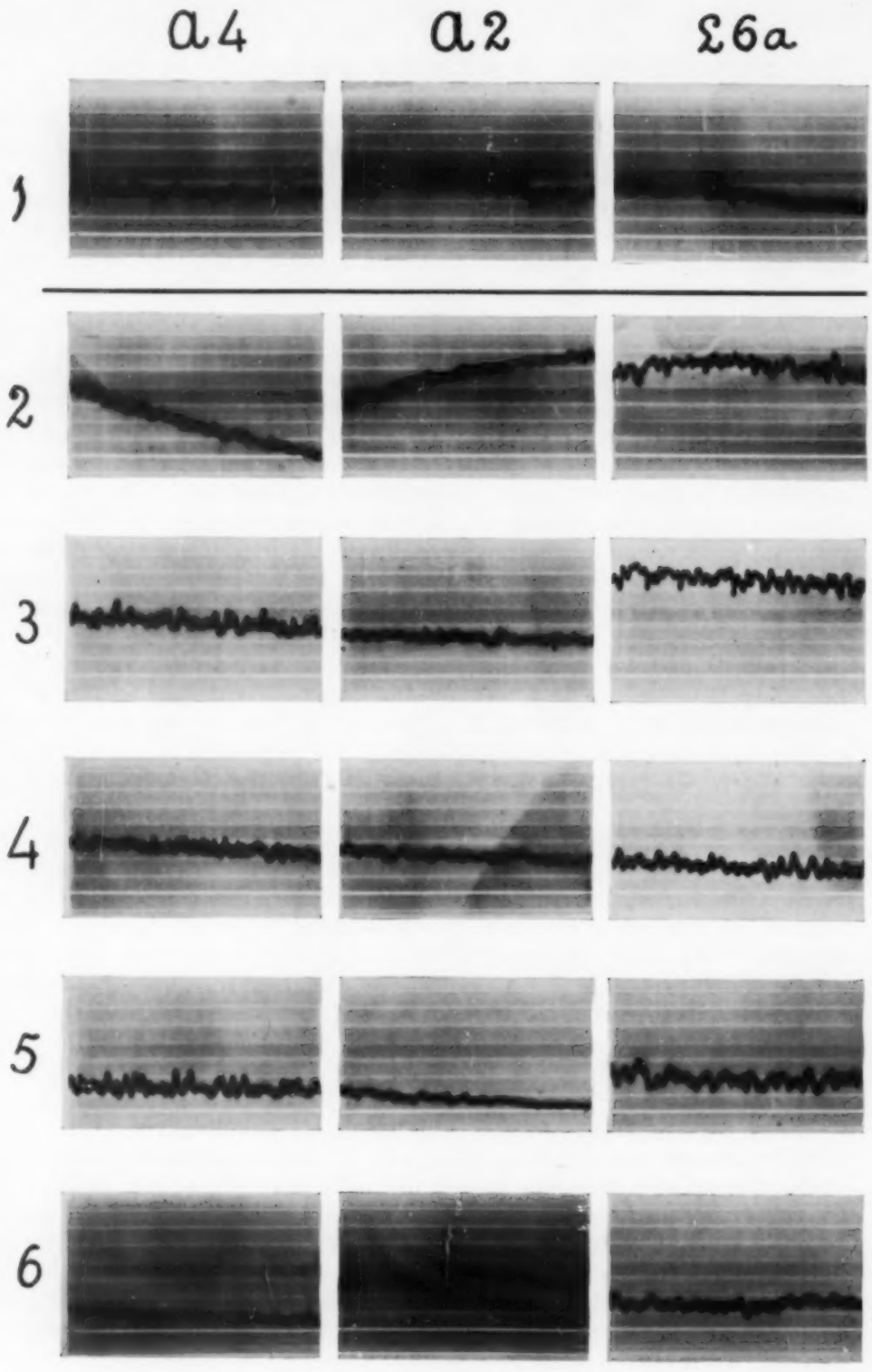
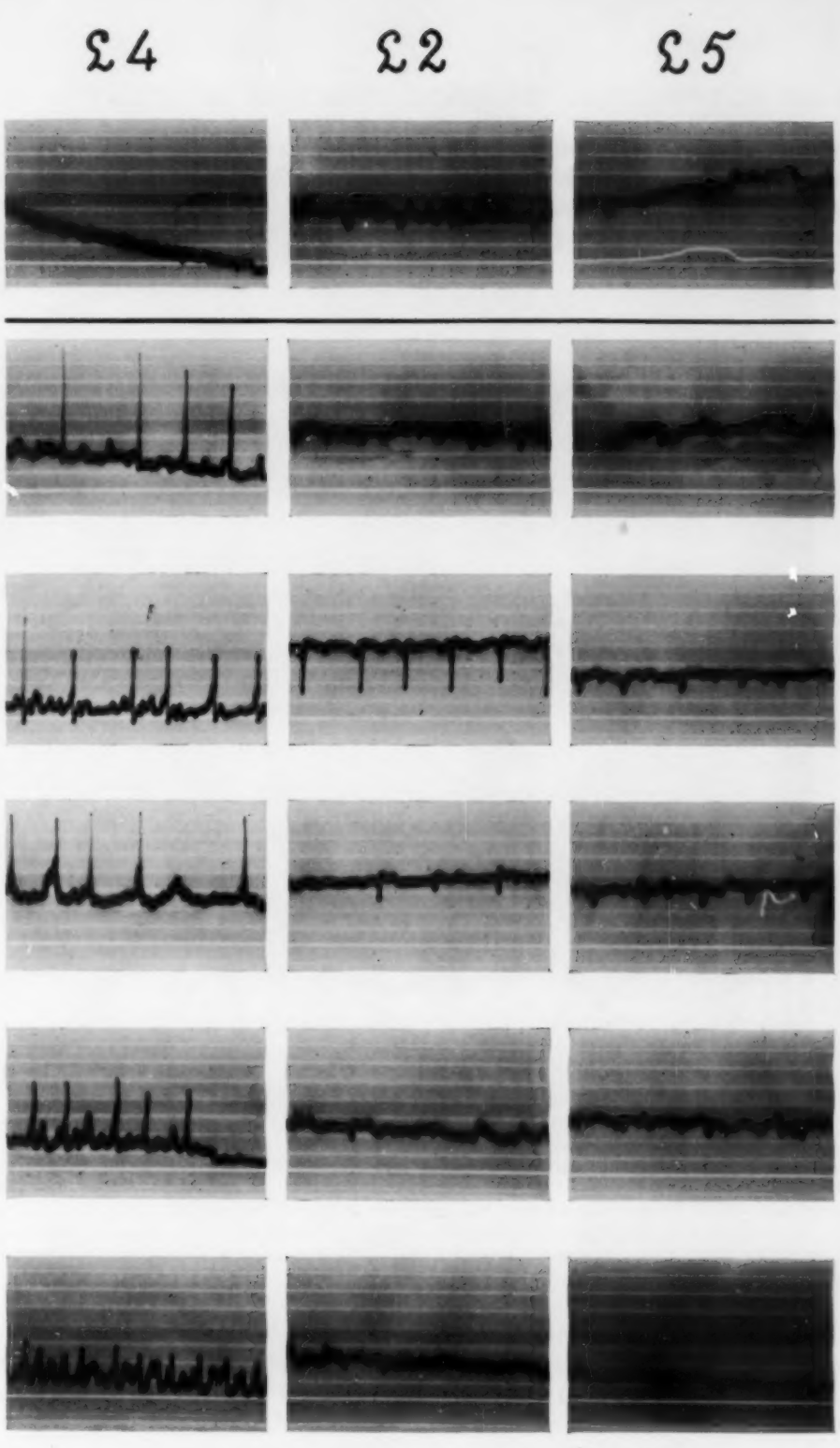


FIG. 5. Experiment of April 23, 1936. Dial-narcosis. Local strychninization of L.4 L.6a, nor in ECGs of A.4 and A.2. Row 1 before, the other rows after the strychninization. gradual return to "normal" from row 4 on.



results in strychnine-spikes in ECG. of L.4, L.2, L.5. No apparent change in ECG. of Time interval between taking of the first ECG. of each row ca 5 minutes. Note also the

electrical stimulation of any one locus of the sensory cortex was essentially the same as the distribution of the strychnine-spikes following local strychninization of this same locus. For this reason it is unnecessary to give the results of these experiments in detail.

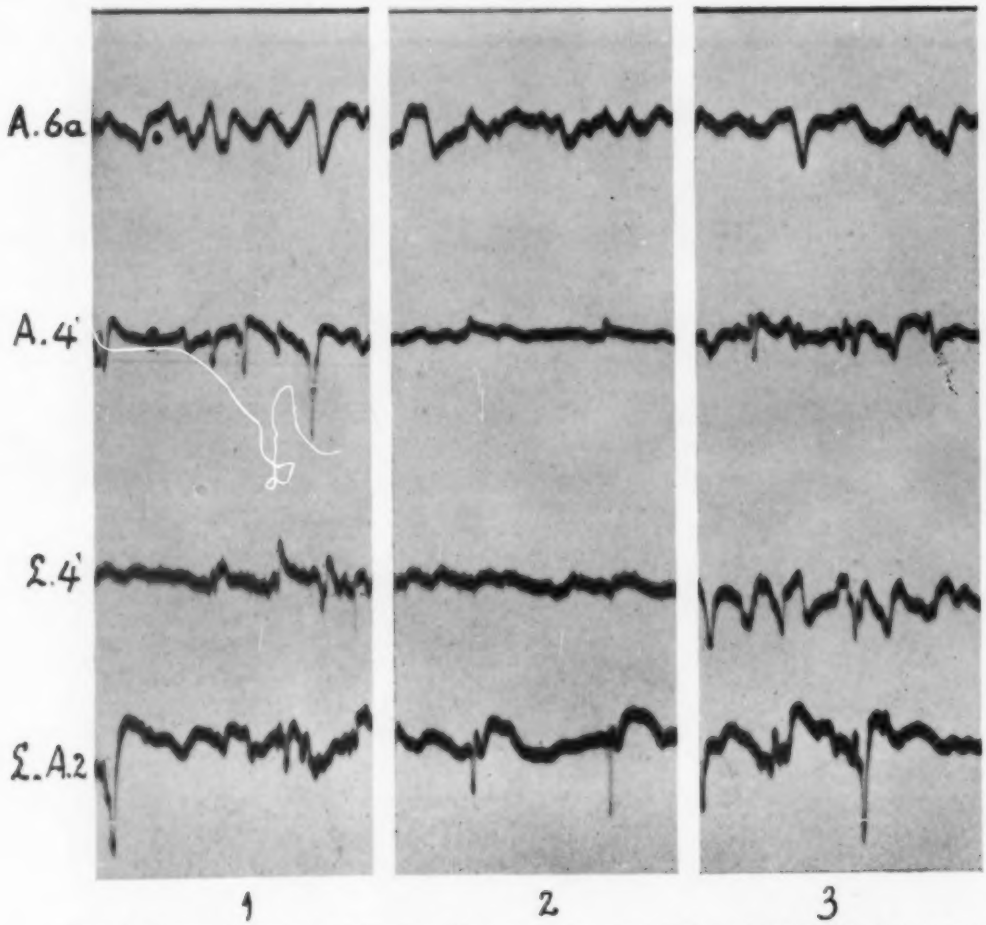


FIG. 6. Figure 6 shows in column 2 the temporary suppression of the ECG. of A.4 and L.4 upon local strychninization of A.4-s. Spikes in postcentral cortex (L-A.2 means that one of the two electrodes was on L.2, the other on A.2). No apparent change in ECG. of A.6a. Records of column 1 before, those of column 2, 7 minutes, and those of column 3, 11½ minutes after the strychninization of A.4-s. Simultaneous ECGs with 4-element Westinghouse oscillograph.

In Figure 8, which shows the distribution of electrical after-discharge in the leg-subdivision of the sensory cortex following appropriate electrical stimulation of a focus of L.4 (4.5 Volt, 5″, 60∼) it will be seen that electrical stimulation of a focus of L.4 produces electrical after-discharge in L.4, L.2, and L.5, but not in L.6a. Comparison with Figure 5 shows the similarity of the

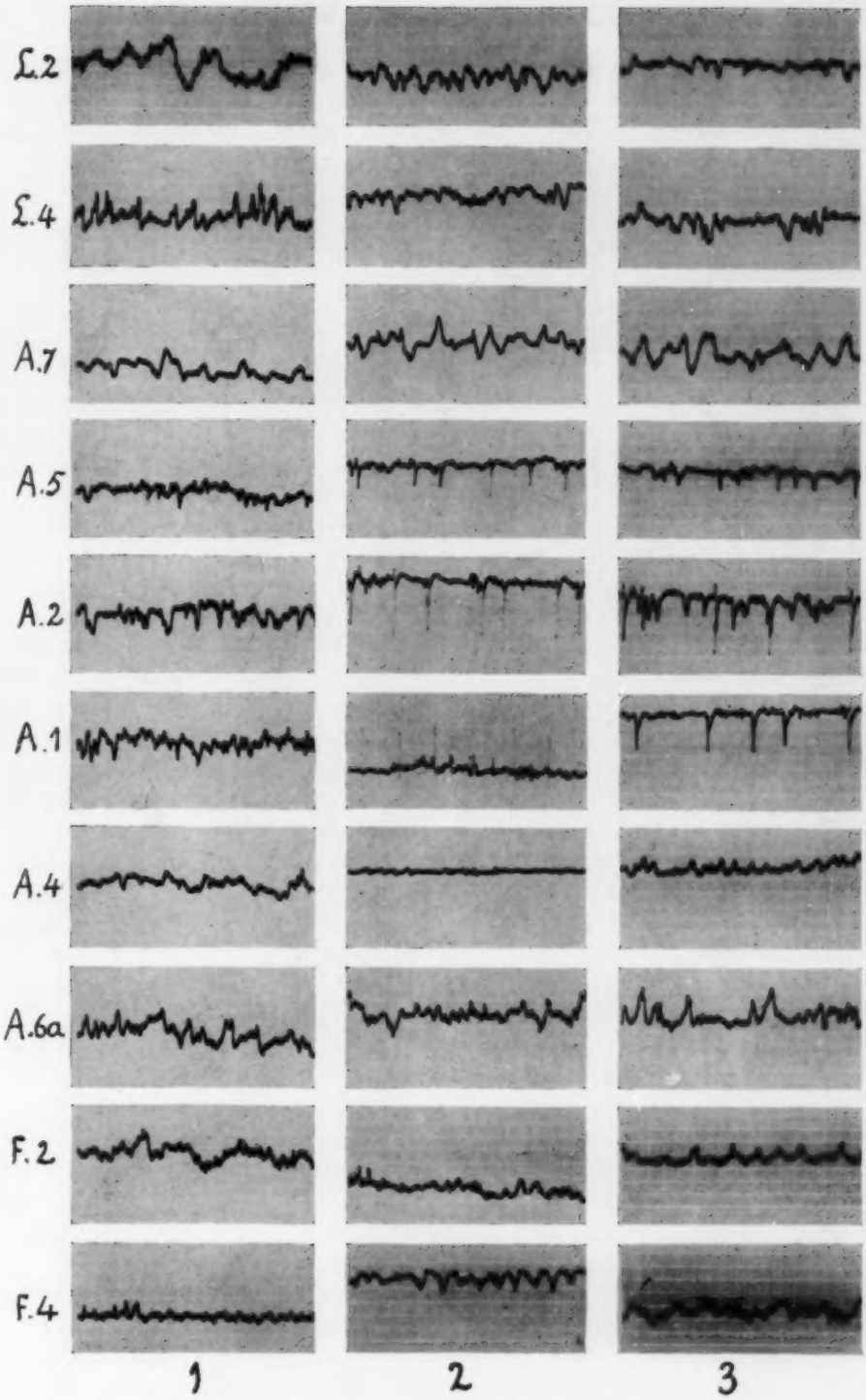


FIG. 7. Figure 7 shows the effect of local strychninization of A.1. Spikes in A.1, A.2, A.5. Temporary suppression of ECG. of A.4 in column 2. No changes in A.6a, nor in L.2, L.4, F.2 and F.4. Return to normal of ECG. of A.4 in column 3. Records of column 1 before, those of columns 2 and 3 after the strychninization.

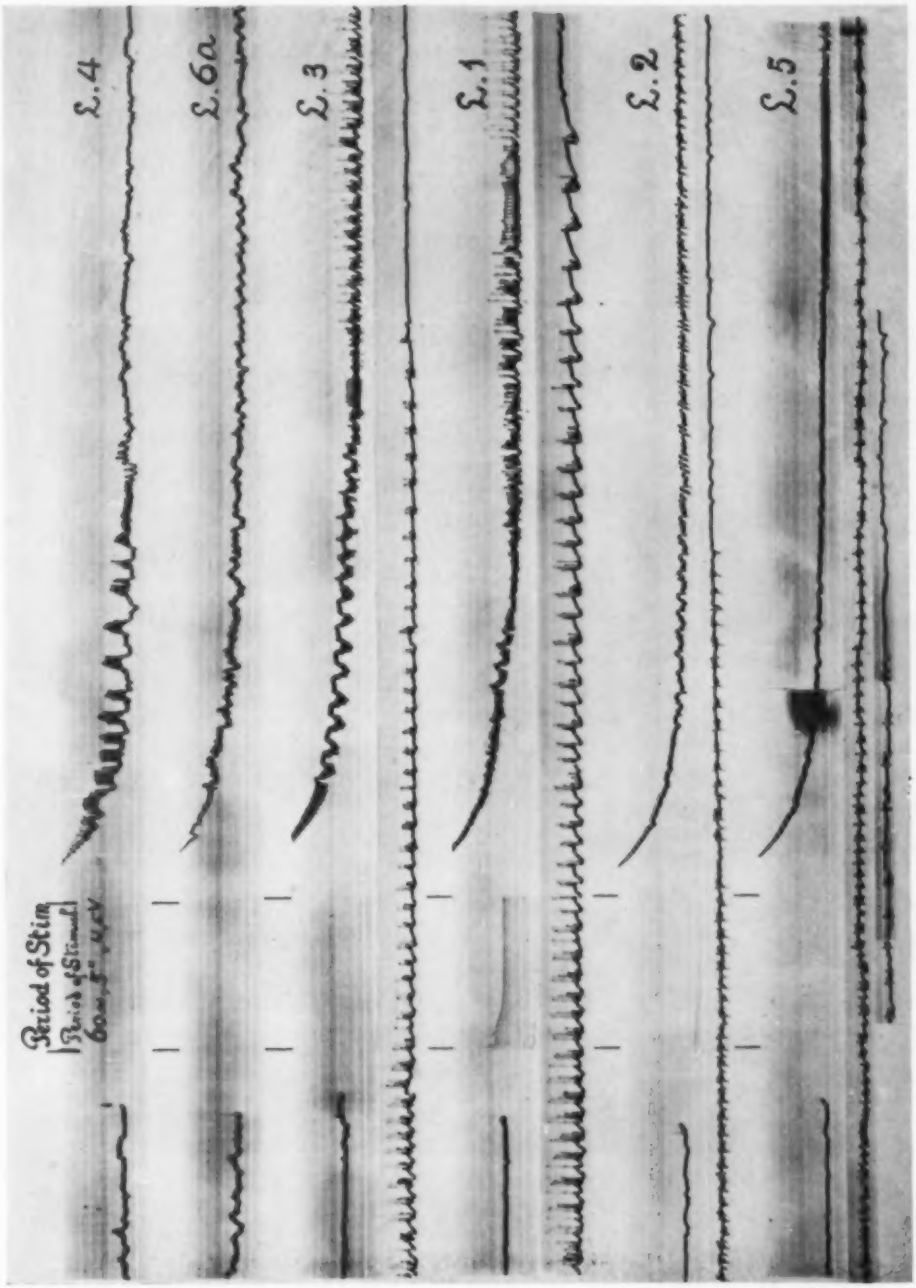


FIG. 8. Experiment of April 23, 1936 on same animal and same foci as of Figure 5. All records taken before and after electrical stimulation (60~, 4.5 V, 4 seconds) of a focus of L.4. Record 1 is ECG. of L.4 itself, 2 that of L.6a, 3 of L.3, 4 of L.1, 5 of L.2, 6 of L.5. Note electrical after-discharge in all records, except in that of L.6a.

distribution of the electrical after-discharge and the strychnine-spikes in these two sets of experiments, obtained by electrical stimulation and local strychninization of one and the same focus, with recording of the ECG. from the same loci in the same cortex of the same animal.

Discussion

The expression that local strychninization of one area "fires," or "sets on fire," this or another area is used purely for convenience to indicate the appearance of strychnine-spikes in this or that area. In 1912 one of us[3] adduced evidence indicating that strychnine produces its remarkable symptoms of sensory excitation, if applied locally to the dorsal horn of the spinal cord, by acting on the nerve cell bodies—the perikarya—within the strychninized area. It is plausible that this holds also for the cerebral cortex, both in regard to the symptoms of sensory excitation and to the typical changes in the ECG. following local strychninization of the (sensory) cortex.

The observation that injection of strychnine into the white matter underneath the cortex—the corona radiata—does not produce sensory symptoms nor strychnine-spikes in the cortex (or the thalamus) is experimental evidence supporting the view that the strychnine produces its remarkable symptoms by action on nerve cell bodies. The fact that essentially similar spikes occur at the site of strychninization irrespective of the cytoarchitectonic structure of the area in question shows that the local functional change induced by the strychnine is uniform throughout the cortex and that the spikes cannot be attributed to the strychninization of any single type of nerve cell. The specific distribution of the spikes encountered in these experiments for any given area strychninized precludes explanation of the findings in terms of any diffusion or absorption of the strychnine. This is in agreement with the older observations, previously adduced by one of us, which all indicate the remarkably local action of strychnine, when applied locally.

When strychnine-spikes appear in various areas upon strychninization within one area these distant spikes are practically simultaneous with the spikes in the area strychninized. Recording on fast-moving film or paper, however, shows that there is a delay of a few sigmas, the longer the greater the distance between the area strychninized and the area from which the spikes are recorded. Whether these propagated, distant spikes are merely axonal action-potentials or whether they reflect also the activity of nerve cells excited by these axons, is not settled. The long duration of the last phase of most of the spikes would seem to indicate that they can not be regarded entirely as pure axonal potentials.

Whatever the explanation of the strychnine-spikes may be, the fact that an area *a* "fires" an area *b*, whereas *b* does not "fire" *a*, must be the expression of *directed* functional relations, and, therefore, directed anatomical relations, between these two areas. Assuming that strychnine produces the spikes by acting on the perikarya of the cortex, the finding mentioned above must be interpreted to mean that nerve cell bodies in area *a* send their axons into area *b*, whereas *b* has no cell bodies the axons of which extend into *a*.

It is possible to make a few general statements about the course of these interareal axons. The distribution of the spikes is not changed by the thermocoagulation of a narrow circular strip of cortex over the entire thickness of the cortex around the strychninized locus nor by deep undercutting of the whole sensori-motor cortex. These findings prove that axons from the area strychninized run through the white matter of the pallium to those other areas in which strychnine-spikes are present. Even within one area, e.g. A.4, circumthermocoagulation of the locus strychninized does not prevent spikes from appearing throughout that area, so that intraareal as well as interareal axons pass through the subjacent white matter. Obviously, these findings do not preclude the operation of intracortical, i.e. intragriseal, axons, but they do show that such axons are not necessary for the apparently normal distribu-

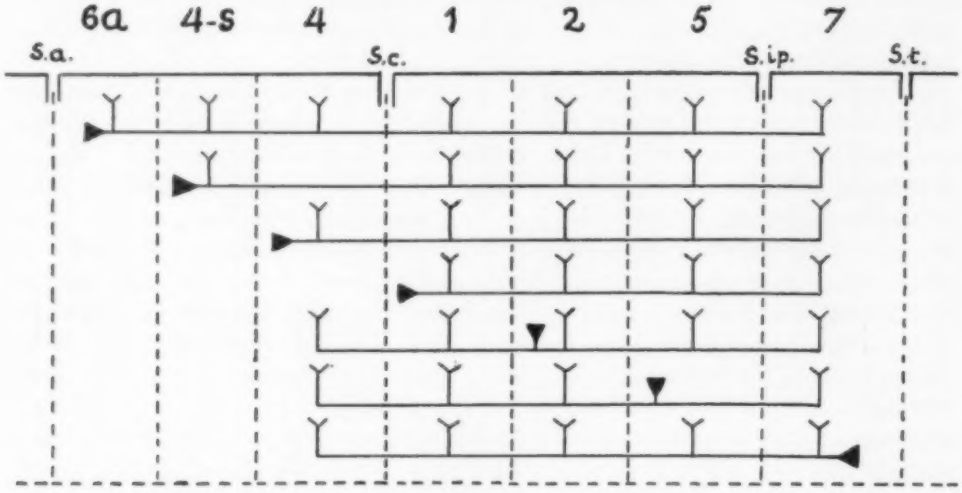


FIG. 9. In Figure 9 are represented diagrammatically the directed functional (and anatomical) relations between the various cortical areas of the arm-subdivision of the sensory cortex found in these experiments. The suppression of the ECG. of area 4 upon local strychninization of area 4-s or area 1 is not represented, because this is not dependent upon cortico-cortical relations.

s.a. = sulcus arcuatus; s.c. = sulcus centralis; s.ip. = sulcus interparietalis; s.t. = sulcus temporalis I.

tion of the strychnine spikes. The specific intraareal and interareal, directed functional relations within the sensory cortex, schematised on the basis of the view that strychnine produces spikes by action on the perikaryon, are given diagrammatically in Figure 9. For reasons of simplicity, the axons are drawn as remaining inside the "griseum" of the cortex, although, as stated in the preceding paragraph, they actually run through the subjacent white matter.

The feature common in the phenomena observable after local strychninization of 6a or 4-s is the appearance of strychnine-spikes in both leg- and arm-subdivisions of the sensory cortex, although the strychninization was performed in only one of the following areas: either L.6a or A.6a, L.4-s or A.4-s.

This means that, so far as the appearance of strychnine-spikes in the ECG. upon local strychninization of these areas is concerned, no functional boundary between the leg- and arm-subdivisions exhibits itself. Furthermore the local strychninization of either L.4-s or A.4-s results, as shown, in a suppression of the ECG. of L.4 and A.4; thus, in this respect, also no boundary appears. These findings contrast with the functional boundaries between these subdivisions of the sensory cortex as they manifested themselves by the distribution of the symptoms of sensory excitation in the experiments on the monkey by one of us in 1924.

This contrast, however, is not a contradiction. The ECG. expresses the activity of the cortex at that level of the CNS, the hypersensitivity depends also upon lower levels, notably the optic thalamus. Experiments in which the electrical activity of the thalamus, the electrothalamogram, was recorded before and after local strychninization of the sensory cortex have provided a satisfactory explanation for the apparent discrepancy mentioned above. The full discussion of this problem must, however, be reserved for a subsequent paper, which deals with the functional interrelation of the sensory cortex and the thalamus.

Our area 4-s lies as a narrow band of cortex in front of L.4 and A.4. The occipital border usually runs from the posterior end of the arcuate sulcus through the posterior portion of the superior precentral sulcus, and continues almost parallel to the central sulcus onto the medial aspect of the hemisphere. This border, however, is more or less arbitrary because of the great variability in size, form and direction of the superior precentral sulcus and of the arcuate sulcus. For the anterior border of area 4-s there is no landmark on the surface of the hemisphere. All we can say on the basis of our physiological observations is that area 4-s is a narrow band of cortex, the width of which measures ca. 2 mm. at its bottom and 3 to 4 mm. at its top.

It should be pointed out that extent and location of area 4-s, as given in Figure 1, should be regarded as an "average" of numerous experiments.

The variability in the pattern of the sulci of the hemisphere of *Macaca mulatta* (and other species) is so great that the location of area 4-s can only be "diagnosed" experimentally. This leads in many experiments to interesting composite, additive results. If the strychnine is applied not strictly within area 4-s, but encroaches upon area 4, this will show up as a combination of a suppression of the ECG. in L.4 and A.4, the part of the symptomatology due to the strychninization of 4-s, with occasional, rather small spikes in L.4 *or* A.4, due to the strychninization of the most anterior part of this area. If the intended strychninization of area 4-s has been performed too much frontally, the most posterior portion of area 6a will also be involved. This will show up by the fact that together with the suppression of the ECG. in area 4, there will appear small spikes in L.4 and A.4 and large spikes in area 6a. Only if the strychninization has been performed "purely" in area 4-s will a "pure" suppression in L.4 *and* A.4 appear without any trace of spikes in these areas or in area 6a. In fact, we have in several animals performed such a series of differently located local strychninizations in this region, thus establishing the exact location and extent of area 4-s in each specimen. Usually area 4-s was found to lie more forward than expected on the basis of examination of the surface configuration, especially on brains in which a large posterior "spur" of the arcuate sulcus is present.

The resemblance in extent and location of area 4-s with the "strip" of

Marion Hines[6] is quite striking. Electrical stimulation of this strip of cortex in her hands abolished existing motor activities, extirpation resulted in spasticity, findings entirely in harmony with the temporary suppression of the ECG. of L.4 and A.4 upon local strychninization of area 4-s. There can be, therefore, no doubt that the "strip" of Hines is identical with our area 4-s. Dr. Hines has written us that she dislikes the colloquial designation of this area as "the strip," an expression having come into use as laboratory slang. The cytoarchitecture of this area, according to Dr. Hines, is similar to that of area 4, but can readily be distinguished from it by the great reduction in the number of Betz cells. It seems advisable and appropriate, therefore, to designate this area as area 4-s.

The cortex in front of area 4-s has the cytoarchitecture of area 6 of Brodmann. Dr. Hines wrote: "And if one is very fussy about cytoarchitecture this area 6 could be divided into two regions again. The pyramidal cells in layer III of the posterior part of area 6 are larger than those found in the same layer of the anterior part of this area." So far we have not been able to find any functional differentiation upon local strychninization of area 6a, and have, therefore, refrained from subdividing it.

If it be permissible to transpose the cortex of *Macaca mulatta* upon that of cercopithecus of the Vogts (species not given so far as we know) it is obvious that our areas 4-s and 6a are not to be identified with the areas 6aα and 6aβ of C. and O. Vogt.

The suppression of the ECG. of L.4 and A.4 by local strychninization of area 4-s is not brought about by cortico-cortical neurons. The experimental evidence upon which this statement rests, will be given in a subsequent paper. The observations presented in this paper confirm the hypothesis advanced by Dusser de Barenne in 1916 and again in 1924 to explain the finding that strychninization of a few square millimeters of the sensory cortex gives rise to symptoms of sensory excitation in a large portion of the body. At that time it was stated "as the most plausible explanation that the strychnine brings the small cortical area poisoned by it into a condition of abnormal and intense hyperexcitability and hyperactivity, and that this condition irradiates from the area poisoned over the whole of that part of the cortex which is in close functional connection with it" [(5) p. 285; see also (4) p. 383]. This assumption has now been proved to be correct in general. The present experiments have revealed details which have been dealt with in this paper.

The method of local strychninization with simple "clinical" observation of the animal failed to reveal functional differentiation within the sensory cortex except for the existence of functional boundaries between its major subdivisions, and, therefore, could not throw further light upon the problem of functional localization within the sensory cortex. The method of local strychninization was used in conjunction with recording of the ECG. with the definite anticipation that this combination of methods would uncover just such finer differences of functional organization in the sensory cortex; this expectation has been confirmed by the experiments presented in this paper. These observations have permitted amplification and specification of the original hypothesis.

Summary

1. The method of local strychninization in combination with that of recording the electrocorticogram (ECG.) has proved suitable for study of the problem of functional organization within the sensory cortex of the monkey.

2. Local strychninization of the cerebral cortex induces typical changes in the ECG., namely the temporary appearance of large and rapid potential fluctuations, or "strychnine-spikes."

3. The distribution of these spikes differs with the locus of strychninization. In the visual cortex (area 17 of Brodmann) and in area 5 of the sensory cortex they are restricted to the area strychninized and its immediate vicinity. In the sensory cortex the spikes are widespread and their distribution specific for different areas.

4. These specific differences in distribution, described in this paper, are the expression of directed relations between the various portions of the sensory cortex, of a functional organization within this region.

5. The local strychninization of two areas of the sensory cortex (areas 4-s and 1) results in a temporary suppression of the ECG. of areas L.4 and A.4, while "firing" other portions of the sensory cortex.

6. Experiments with recording of the ECG. and local electrical stimulation of various areas of the sensory cortex showed that the distribution of the propagated excitation, manifesting itself in the spread of an electrical afterdischarge, was the same as the distribution of the spikes elicited by local strychninization of these same areas.

7. The observations reported here confirm and amplify the original hypothesis of one of us of an intimate functional interrelation of the various areas within any one major subdivision of the sensory cortex.

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